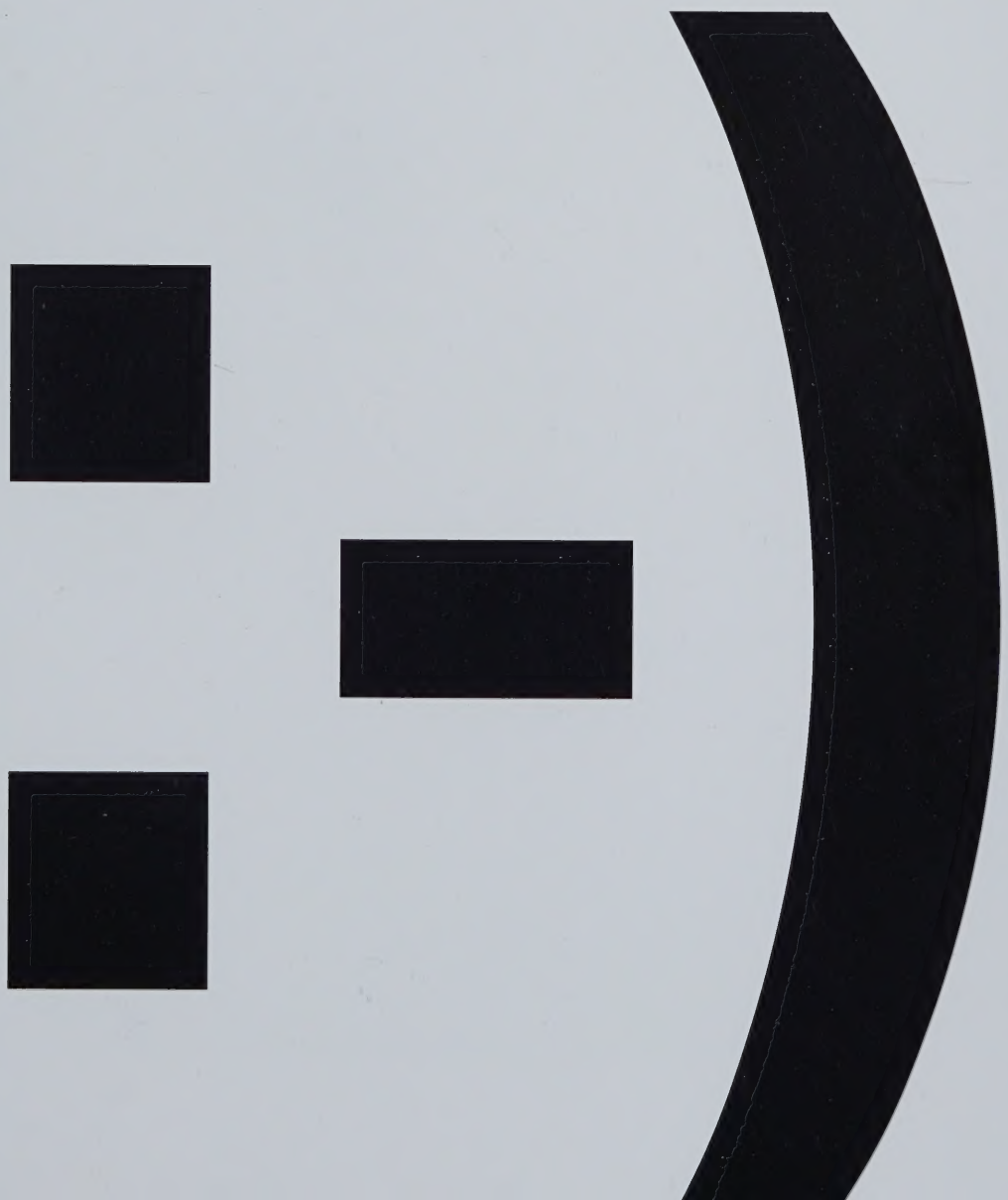
Harvard Medicine

SUMMER 2011

The science of emotion



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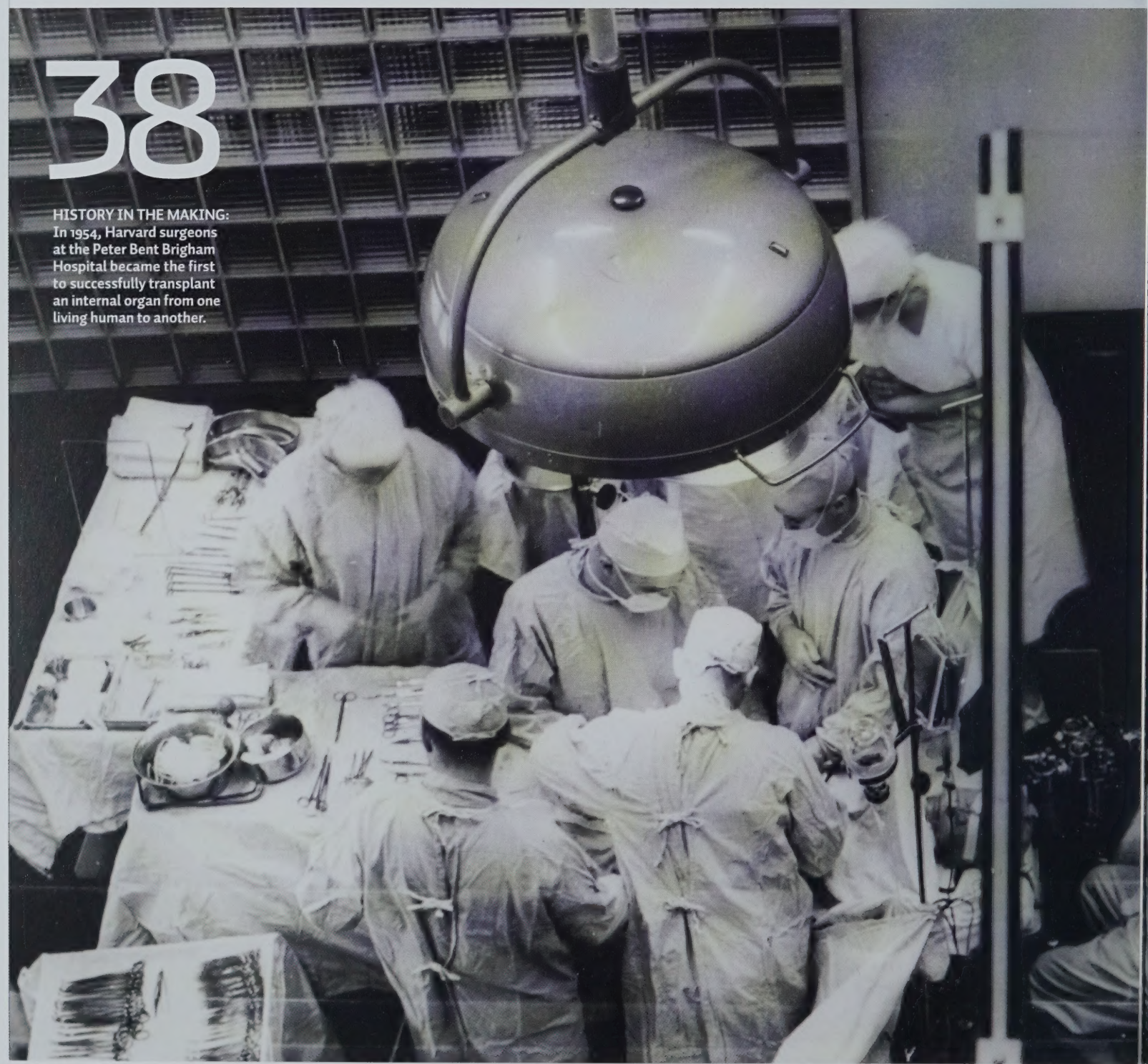

HISTORY IN THE MAKING: In 1954, Harvard surgeons at the Peter Bent Brigham Hospital became the first to successfully transplant an internal organ from one living human to another.

Special Report: The Science of Emotion

Features

Departments

From the Dean

THOUGHTS ON INNOVATION

Emotion has long been the province of poets. The oldest recorded love ballad, in fact, was scratched onto a Sumerian clay tablet more than four millennia ago. So why are today's scientists meddling with the mysteries of love, melancholia, and joy? What prompts researchers to subject our passions to the dispassionate tools of biomedical science?

This issue of *Harvard Medicine* is devoted to exploring the ways in which Harvard Medical School investigators are using those tools—brain scans, protein analyses, clinical trials—to understand and mitigate human suffering.

In this issue you'll read about techniques for treating intractable depression, for easing the pain of post-traumatic stress disorder, for softening adolescent rage. You'll gain insight into the neurological links between anger and depression. And you'll learn that love is not a secondhand emotion, but an elemental one, as essential to our well-being as sleep and nourishment.

In a playful counterfoil to this special report on emotion, you'll also find an exploration of what science fiction can teach us about science fact. In this feature, scientists describe, tongue in cheek, the inspiration they've derived from creatures decidedly lacking in feelings: zombies, extinct beasts, and the elfin-eared Spock.

Regrettably, I note that this issue of the magazine is the last under the editorship of Paula Byron. For a dozen years Paula led a series of creative teams in producing issues that explored medicine through a range of themes, from the neurobiology of the arts to the seven deadly sins, from ethics to fashion, from history's medical mysteries to the five senses. During that time the magazine was named a finalist for the National Magazine Award and won more than 30 national awards for editorial excellence, including the Robert Sibley Magazine of the Year Award. More important than awards, though, was Paula's rich collaboration with the graduates, faculty, staff, and students at HMS. We wish her success in her new role at Virginia Tech, where, after years of telling the stories of one of the nation's oldest medical schools, she'll be telling the stories of one of the youngest.

Our regret over this change should be tempered, however, by the knowledge that this fine magazine will continue, its voice remaining a strong and vibrant one for the School and its alumni.

Jeffrey S. Flier
Dean of the Faculty of Medicine
Harvard Medical School

HarvardMedicine

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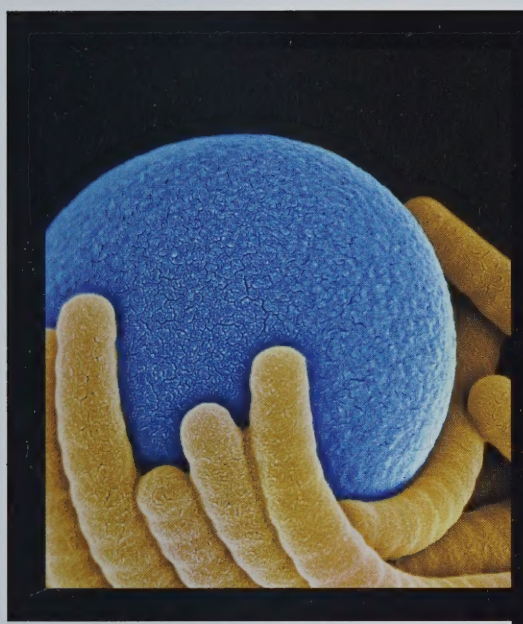
Letters to the Editor

SECOND OPINIONS FROM OUR READERS



The Twilight Zone

Regenerative cells, preimplantation genetics, reprogrammable adult stem cells, small RNA messengers—this is stuff out of *Buck Rogers!* It makes me want to get back to the lab.

ARMAND LEFEMINE '52
CENTERVILLE, MASSACHUSETTS

The Final Frontier

Your latest issue of *Harvard Medicine* was outstanding. I particularly enjoyed "The Twilight Zone," with its far-out science. Regenerative cells, preimplantation genetics, reprogrammable adult stem cells, small RNA messengers—this is stuff out of *Buck Rogers!* It makes me want to get back to the lab!

ARMAND LEFEMINE '52
CENTERVILLE, MASSACHUSETTS

A Man After Our Own Hearts

I received the Spring 2011 issue of *Harvard Medicine* today, and I struggled to understand much of the technological information that has evolved since my days of being actively involved in the study and practice of medicine. I had no trouble, though, understanding "They All Laughed," Jessica Cerretani's biographical accounts of HMS faculty and graduates whose theories, considered outlandish at the time, proved to be right.

I was particularly interested in the story about Paul Zoll '36 and the reintroduction of cardiac pacing. I was reminded of the time he visited Montefiore Hospital in the Bronx in 1959, when I was chief medical resident. Dr. Zoll's reputation had already been established as the developer and proponent of external cardiac pacing, but he came to see what one of my fellow surgical residents had developed for the treatment of complete heart block.

The surgical resident was Seymour Furman, known best as "Sy." He presented a patient to Dr. Zoll and explained that while doing a research rotation as part of his training, he had implanted in the patient a transvenous stimulator that was connected to a bulky external source of power. The stimulator was portable and required only minimal electrical stimulation, so it was much more practical than Dr. Zoll's device, which caused the chest wall to contract with each pulsation.

As a true gentleman, Dr. Zoll proclaimed that Dr. Furman's device was an outstanding contribution to the world of medicine. The contributions of both these doctors, in fact, led to the evolution of today's great implantable devices.

ROBERT J. SPERBER '55
MAMARONECK, NEW YORK

Quality Time

The opening premise of your short article on ibuprofen—that it may have a protective effect against Parkinson's disease—should surprise no one who understands that many, if not most, chronic degenerative diseases are a result of oxidative stress. And if it does seem remarkable, it should be seen as further proof of that view on degenerative disease. Yet artificial antioxidants like ibuprofen have bad side effects. Natural antioxidants provide the same result and more, without the negative consequences. That's why many chronic diseases can also be seen as chronic nutritive deficiencies, and why their symptoms improve with supplementation with quality multivitamins and multiminerals—those with high bioavailability and high purity.

BRAD LICHTENSTEIN
CAMBRIDGE, MASSACHUSETTS

An Honor and a Privilege

The Spring 2011 issue is a triumph!

MITCHELL T. RABKIN '55
BOSTON, MASSACHUSETTS

Harvard Medicine *welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *107 Avenue Louis Pasteur, Suite 111, Boston, Massachusetts 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity. The magazine also welcomes ongoing feedback through its Readers' Panel. To become a member, visit harvardmedicine.hms.harvard.edu/feedback.php.*

SEARCH AND RESCUE: Before graduating from Harvard Medical School this past spring, Belinda Waltman helped Massachusetts General Hospital researchers identify genetic changes that occur in lung cancer, with the hope of creating new drugs to combat the disease.

CURIOSITY SEEKERS

The Scholars in Medicine Program nurtures a love of discovery

HARVARD MEDICAL SCHOOL will soon launch a new component of medical education reform: the Scholars in Medicine Program. Starting with the class entering this fall, every medical student will be required to undertake a scholarly project. According to the program's director, Gordon Strewler '71, projects will run the gamut of inquiry, from molecular biology to the history of medicine.

The goal, Strewler says, is to hone students' critical thinking and foster curiosity while equipping them with tools for discovery. "Students will not only master knowledge, but also help create it—in the form of a written work, perhaps even a publication," says Strewler, an HMS professor of medicine at Beth Israel Deaconess Medical Center.

First-year medical students will identify a mentor and an idea for a summer scholarly project, then submit a proposal. While this effort may evolve into a definitive project, one that will take four to twelve months to complete, students have the option of pursuing a different project later on, perhaps one related to a joint degree.

"Faculty and students alike can reap tremendous rewards from the bonds that form while working together," Strewler says. "Were it not for my own mentors, I might never have studied endocrinology."

According to HMS Dean Jeffrey Flier, faculty engagement in the program promises rewarding returns from ambitious, creative students. "It's often said that science is a family tree, and that every scientist descends from a unique pedigree of mentors and advisors," Flier says. "In turn, we leave a legacy—not only our ideas and discoveries, but also a group of trainees to whom we have passed the torch. At this great medical school, we have a rich tradition of paying our debt of knowledge forward."

—Karin Kiewra

Cowboys, Pit Crews, and a Bit of Dr. Seuss

Class Day inspires optimism for the future of medicine

WITH THEIR NEWLY INKED diplomas in hand, the recent graduates of Harvard's medical and dental schools relished their accomplishments, and the sunshine, of Class Day 2011. Families, friends, and faculty looked on as several speakers underscored the optimism and joy of the occasion, while reminding the graduates of their unprecedented opportunity to improve not only their patients' lives but also the health care system they will inherit.

James Sawalla Guseh II '11 set the stage for the other speakers' philosophical musings with his own glimpse into the future of his fellow new physicians with a clever retooling of Dr. Seuss's *Oh, the Places You'll Go!* Wielding his poetic license in advance of his medical license with "Oh, the Doctors You'll Be!," Guseh dispensed the medicine of laughter with verses such as: "What's your chief complaint?/I ask and you share,/What's that you say?/A hernia repair?/Does it itch? Does it burn?/Does it tingle down there?/That must be hard for you./Are you feeling despair?/Do you need medical advice?/I better send you elsewhere,/because I'm a medical student./I'll be a doctor next year."

Anjana Sharma '11 spoke eloquently about her own and her classmates' experiences surviving medical school. Her address started with the common fear of many successful, accomplished people—that their achievements are partly the result of a clerical error.

Speaking of the sacrifices their families made to get the graduates to this day, the faculty and staff who inspired and served as role models, the patients who taught them most of all, and the camaraderie of peers, Sharma emphasized that their relationships are what will make them better doctors. "Let's stay close," she said. "Let's stay accountable to each other, and let's work together to reshape a broken health care system."

Commencement speaker Atul Gawande '94, an HMS associate professor of surgery, echoed Sharma's call to join forces for better patient care. After noting how the practice of medicine has changed over the past generation or two, Gawande expressed his appreciation of the undeniably positive effects of treatment advances. At the same time, he said, the increasing complexity of medicine has "exceeded our individual capabilities as doctors."

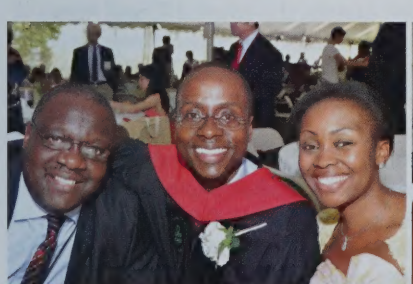
He went on to talk about the "cusp point in medical generations"—where the graduating students will soon find themselves, and where they may find great opportunity. The health care system has become fragmented and segregated into silos to the point, he said, that no one person can know everything about a specific patient's treatment.

"It's like no one's in charge—because no one is," he said. "We train, hire, and pay doctors to be cowboys. But it's pit crews people need." And places that provide the most successful care are those in which the team functions as a system, in which all involved in a patient's care "actually work together to direct their specialized capabilities toward common goals for patients. They are coordinated by design. They are pit crews."

Physicians have traditionally been trained to be autonomous, independent, and self-sufficient. While these qualities are admirable, Gawande said, the pit-crew approach requires humility, knowledge that failure is inevitable, and teamwork.

Gawande exhorted the graduates to consider these values as they embark on their medical careers. Shifting from corralling cowboys to producing pit crews, he reminded them, "is the great task of your and my generation of clinicians and scientists."

—*Susan Karcz*




OH, THE PLACES THEY'LL GO: Members of the HMS Class of 2011 celebrated their graduation just weeks before beginning residency training. Eighty-seven members of the class will stay at a Harvard-affiliated institution for at least part of their training. Twenty-nine will head to California, and 17 will train in New York City.

FRESH START: Just hours after giving birth, a young mother watches her baby sleep at a maternity hospital in Port-au-Prince, Haiti, on New Year's Day of 2011.

Minding the Gap

New programs target underserved populations worldwide

AN ESTIMATED 99 percent of infant deaths worldwide occur among socially and economically disadvantaged populations. Nearly two-thirds of these deaths result from conditions that could be prevented by simple, low-cost, noninvasive treatments unavailable in poorer countries.

Tackling such health inequities is the mission of the Programs in Global Health and Social Change, launched last year by the Department of Global Health and Social Medicine at HMS. By marshalling the scholarly expertise of the School, its affiliated institutions, and nongovernmental organizations, these programs aim to demonstrate the level of innovation possible when enough skill and commitment are brought to bear on unmet burdens of disease in resource-poor settings.

"These programs integrate research, service, and training to build the empirical base to address complex problems in global health: what works, what's effective, and what's locally acceptable," says Anne Becker '90, the Maude and Lillian Presley Professor of Global Health and Social Medicine. "We're placing particular emphasis on the clinical areas of greatest unmet need, including the chronically under-resourced areas of children's health and mental health."

The Program in Newborn Health and Social Change, developed in collaboration with the Brigham and Women's Hospital Division of Global Health Equity and Partners In Health, provides one example.

"We're starting with the recognition that all children, but especially newborns and infants, are particularly vulnerable," says Sadath Sayeed, program director and HMS instructor in social medicine. "And we're focusing our interventions on the health and well-being of a newborn's greatest ally, his or her mother. This year, for instance, two of our Harvard-based physicians will begin interviewing women at a maternity clinic in Haiti's Central Plateau, one of the poorest regions in the poorest country of the Western Hemisphere. Through the interviews, the doctors hope to better understand the challenges these women face in obtaining health care and to gauge their interest in participating in a community-based empowerment approach."

—Susan Karcz

A New Pain Barrier

Harvard launches a virtual forum to advance treatments

CHRONIC PAIN disrupts the lives of one of every four people in the United States and costs the nation $80 billion annually in lost productivity. Yet effective treatments to counter persistent pain have been lacking. That therapeutic dearth will now be addressed with the launch of the Pain Research Forum. A joint effort of the Harvard NeuroDiscovery Center (HNDC) and the MassGeneral Institute for Neurodegenerative Disease (MIND), the forum is an interactive virtual community for researchers and clinicians who study chronic pain.

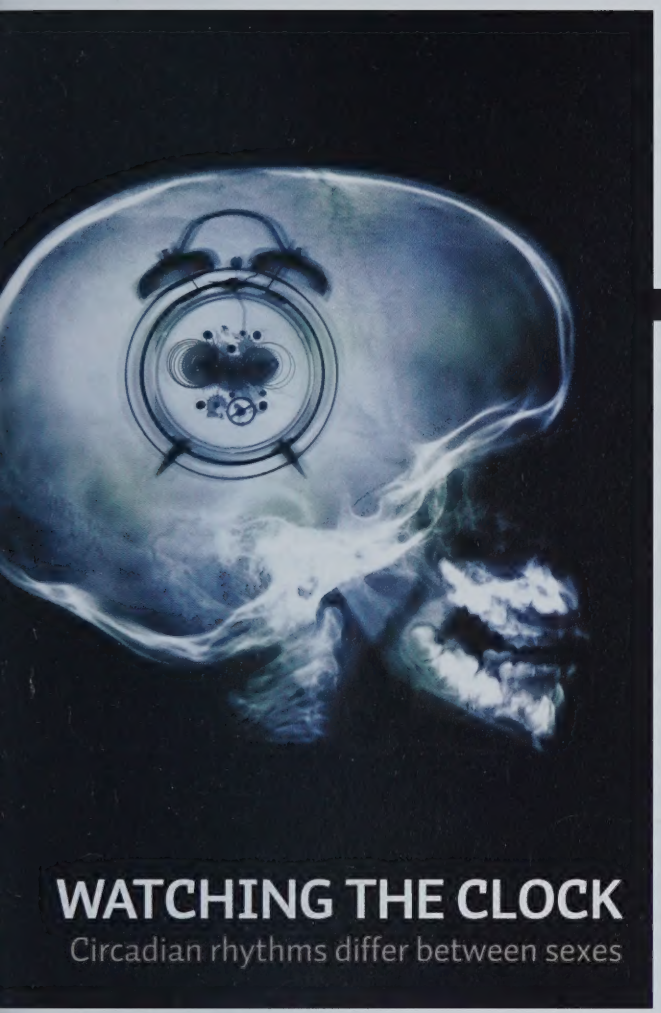
"Highly interactive web communities are an increasing part of day-to-day communication for users of the Internet," says Adrian Ivinson, director of the Harvard NeuroDiscovery Center. "But they are relatively rare in the research community. We hope the Pain Research Forum will become an agora of information and ideas for researchers in the field and that their interactions will catalyze novel, collaborative, and ultimately successful approaches to the challenge of discovering and developing new treatments for chronic pain."

Despite 40 years of progress in understanding the molecular mechanisms and neurobiological underpinnings of pain, few discoveries have been translated into new treatments or other patient-relevant advances.

"Pain is a fragmented clinical field in terms of both research and treatment," says Joseph Martin, the Edward R. and Anne G. Lefler Professor of Neurobiology at HMS, co-founder of HNDC, and a science advisor to the Pain Research Forum. "We hope this site will encourage researchers and clinicians to cross specialty and disciplinary boundaries to work together on improving the care of patients."

The online tool provides news, discussion forums, and research resources. To learn more, visit painresearchforum.org.

—Pat McCaffrey



WATCHING THE CLOCK

Circadian rhythms differ between sexes

THE BRAIN'S circadian clock cycles at a faster pace in women, which may help account for why women tend to wake earlier and are more likely than men to experience sleep maintenance insomnia, according to research at Brigham and Women's Hospital. The findings, which remained consistent for both younger and older men and women, were published May 2 online in the *Proceedings of the National Academies of Science.*

The researchers measured the cycle length of the circadian timing system of 52 women and 105 men aged 18 to 74. The study participants were each studied for two to six weeks on a special schedule in an environment shielded from external time cues to assess the cycle time of his or her brain's circadian clock. The researchers found that the natural circadian cycle of individual participants ranged from about 23-and-a-half hours to 24-and-a-half hours, and that age did not have an effect on the duration of the cycle. The researchers also found that the circadian cycle length in both men and women averaged slightly longer than 24 hours, but the circadian cycle of the women averaged some six minutes shorter than that of the men, and women were two and a half times more likely than men to have cycles shorter than 24 hours.

"The findings are important in that they show a true sex difference in the brain's circadian clock between people," says Charles Czeisler, chief of the Division of Sleep Medicine at Brigham and Women's Hospital. "Knowing this can help in tailoring sleep therapies based on sex."

"The shorter circadian cycle in women," says Jeanne Duffy, lead author of the study and an HMS associate professor of medicine, "may be due to higher levels of estrogen, although we need to do further research to understand why women's circadian cycles tend to be shorter than those in men."

Family Quicksilver

Poor emotional control runs in some families with attention deficit hyperactivity disorder

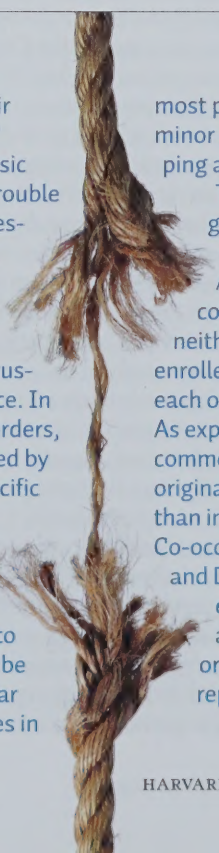
SOME ADULTS with attention deficit hyperactivity disorder, or ADHD, also exhibit excessive emotional reactions to everyday events, and this combination of ADHD and emotional reactivity appears to run in families. A study from a Massachusetts General Hospital–based research team finds that siblings of people with both ADHD and deficient emotional self-regulation (DESR) have a significantly greater risk of having both conditions than did siblings of those with ADHD alone. The study appears in the June issue of the *American Journal of Psychiatry.*

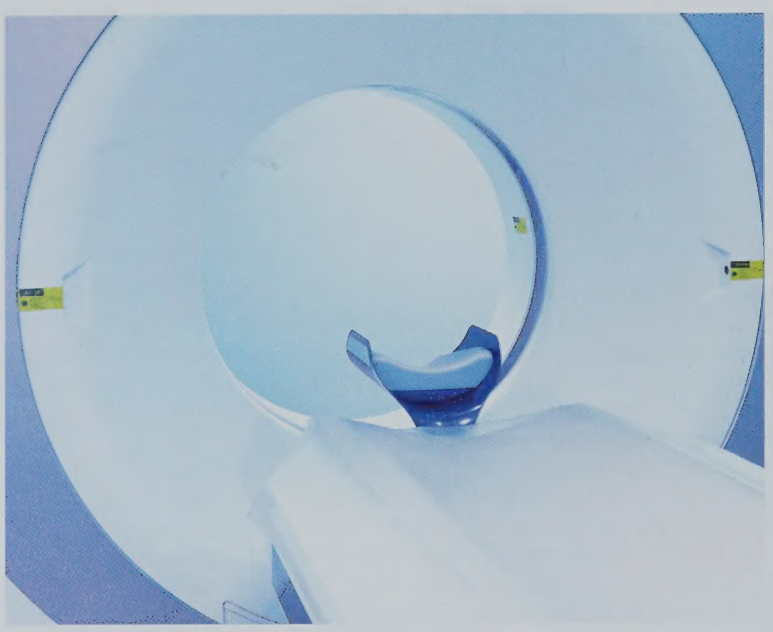
"Our research offers strong evidence that heritable factors influence how we control our emotions," says Craig Surman, an HMS instructor in psychiatry at Mass General and the study's lead author. "Emotion—like capacities such as the ability to pay attention or control physical movement—is probably under forms of brain control that we are just beginning to understand. Our findings also indicate that ADHD doesn't just impact things like reading, listening, and getting the bills paid on time; it also can impact how people regulate themselves more broadly, including their emotional expression."

Along with the classic ADHD symptoms of trouble paying attention, excessive physical activity, and poor impulse control, many people with ADHD display high levels of anger, frustration, and impatience. In contrast to mood disorders, which are characterized by the persistence of specific emotions and behaviors, DESR involves emotional expressions that are brief and occur in reaction to situations that would be expected to produce far less extreme responses in most people, such as reacting to minor disappointments by snapping at family members.

The study began with a group of 83 participants—23 with ADHD alone, 27 with ADHD plus DESR, and 33 comparison participants with neither condition—and then enrolled one or more siblings of each of the original participants. As expected, ADHD was more common in the siblings of the original participants with ADHD than in the comparison group. Co-occurrence of both ADHD and DESR was found almost exclusively, however, among siblings of the original participants who reported both conditions.

—Sue McGreevey





BRAIN TEASERS

Many children with head injuries can forgo CT scans

ROUGHLY HALF OF U.S. CHILDREN taken to emergency departments for a head injury receive a CT scan, often to ease parents' concerns. Yet true traumatic brain injury is uncommon. A multicenter study of more than 40,000 children with minor blunt head trauma, led by Children's Hospital Boston and UC Davis, shows that allowing a period of observation can reduce the use of head CT by as much as half without compromising care—and without exposing children to ionizing radiation. Results appear in the June issue of *Pediatrics*.

"Only a small percentage of children with blunt head trauma really have something serious going on," says Lise Nigrovic, an HMS assistant professor of pediatrics at Children's Hospital Boston, who co-led the study with Nathan Kuppermann, chair of the Department of Emergency Medicine at UC Davis. "If you can be watched in the emergency department for a few hours, you may not need a CT."

After analyzing the outcomes of children at 25 different emergency departments, Nigrovic, Kuppermann, and colleagues found that the children who were observed had a lower rate of CT than those not observed. When the researchers matched the observed and nonobserved groups for severity of head injury and hospital practice style, this difference was more pronounced: The likelihood of a CT scan in the observed group was about half that of similar nonobserved patients. In particular, children whose symptoms improved during observation were less likely to eventually be scanned.

Allowing for an observation period did not compromise safety, the study found: Clinically important traumatic brain injury—resulting in death, neurosurgical intervention, intubation for more than 24 hours, or hospital admission for two or more nights—was equally uncommon in the observed and nonobserved groups (0.75 versus 0.87 percent).

Nigrovic and Kuppermann note that cranial CT scans present risks for children, whose growing brain tissue is more sensitive to ionizing radiation than that of adults. "There is a clear need to develop appropriate and safe guidelines for decreasing the number of inappropriate head CT scans that we do on children," says Kuppermann. "The results of this analysis demonstrate that a period of observation before deciding to use head CT scans on many injured children can spare children from inappropriate radiation while not increasing the risk of missing important brain injuries."

Forces of Nature

After a decades-long quest, scientists have found the protein that drives mitochondria

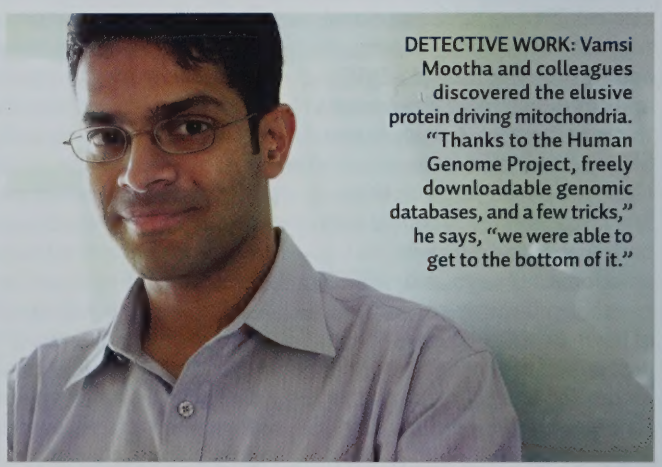
MITOCHONDRIA, those battery-pack organelles that fuel the energy of nearly every living cell, have an insatiable appetite for calcium. The mitochondria of most organisms eagerly absorb this chemical compound. Because calcium levels link to many essential biological processes—not to mention conditions such as neurological disease and diabetes—scientists have been working for half a century to identify the molecular pathway that enables these processes.

After decades of failed effort that relied on classic biochemistry and membrane protein purification, Vamsi Mootha, an HMS professor of systems biology at Massachusetts General Hospital, and colleagues have discovered the linchpin protein that drives mitochondria's calcium machinery. Their findings appeared online in *Nature* on June 19.

With their earlier discovery of MICU1, a protein essential for calcium uptake, as a point of reference, the researchers scoured a range of genomic databases for proteins whose activity profile mirrored that of MICU1. One protein with no known function stood out. The researchers named it mitochondrial calcium uniporter, or MCU.

"Scientists studying the nexus of energy metabolism and cellular signaling will be particularly interested in MICU1 and MCU," says Mootha. "It's still very early, but these proteins could prove to be valuable drug targets for diseases ranging from ischemic injury and neurodegeneration to diabetes."

— David Cameron



DETECTIVE WORK: Vamsi Mootha and colleagues discovered the elusive protein driving mitochondria. "Thanks to the Human Genome Project, freely downloadable genomic databases, and a few tricks," he says, "we were able to get to the bottom of it."

A WHOLE DIFFERENT ANIMAL: David Reich's work in genetics often uncovers unexpected findings. Recently, for example, he and colleagues found that Africa has two distinct elephant species.

MAP OF THE WORLD

A new biological atlas focuses on African American genomics

A CONSORTIUM LED BY SCIENTISTS at the University of Oxford and Harvard Medical School has constructed the world's most detailed genetic map.

A genetic map specifies the precise areas in the genetic material of a sperm or egg where the DNA from the mother and father has been reshuffled in order to produce this single reproductive cell. The biological process whereby this reshuffling occurs is known as recombination. While almost every genetic map built so far has been developed from people of European ancestry, this new map is the first constructed from recombination genomic data of African Americans.

"This is the world's most accurate genetic map," says David Reich, an HMS professor of genetics, who co-led the study with Simon Myers, a lecturer in the Department of Statistics at the University of Oxford.

The researchers were surprised to find that positions on the map where recombination occurs in African Americans differ significantly from those in non-African populations.

"More than half of African Americans carry a version of the biological machinery for recombination that is different than Europeans," Myers says. "As a result, African Americans experience recombination where it almost never occurs in Europeans."

These findings—and the ability to map these genes more precisely—are expected to help researchers both understand the roots of congenital conditions that occur more often in African Americans and discover new disease genes in all populations.

"The places in the genome where there are recombination hotspots can also be disease hotspots," says Reich. "Charting recombination hotspots can thus identify places in the genome that have an especially high chance of causing disease."

The findings appear in the July 21 issue of *Nature*.

—*David Cameron*

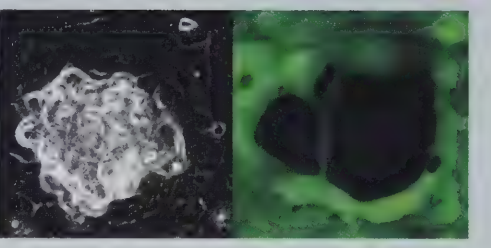
What's Your Emergency?

Health care reform may account for a drop in low-severity emergency department visits

WHILE OVERALL EMERGENCY department (ED) use in Massachusetts continues to rise, the number of low-severity visits dropped slightly since implementation of the state's mandatory health care coverage law, according to an *Annals of Emergency Medicine* study published online in June.

"Our study suggests other factors play a role in determining access to care and use of the ED in addition to one's insurance status," wrote Peter Smulowitz, the study's lead author and an HMS instructor in medicine at Beth Israel Deaconess Medical Center. "These likely include availability of primary care, convenience of ED hours, and the ability to obtain a comprehensive evaluation and testing at one time in the ED." Smulowitz added that it may take patients time and effort to alter their care-seeking patterns.

The small decrease in low-severity visits was contrary to expectations before the implementation of reform, Smulowitz wrote. "To the extent that policymakers expected a substantial decrease in overall and low-severity ED visits, this study does not support those expectations."



SECRETS REVEALED: Ovarian cancer cells (top left) use physical force to push their way through a layer of mesothelial cells (shown in green), leaving the cell layer with a gaping hole.

Dodging a Bully

Ovarian cancer cells use brute force to permeate tissue

A TEAM LED BY JOAN BRUGGE, chair of the HMS Department of Cell Biology, has shed light on how ovarian cancer spreads. In a paper published in the July issue of *Cancer Discovery*, Brugge and colleagues found that ovarian cancer cells act like bullies, using brute force to plow their way through tissue and colonize additional organs.

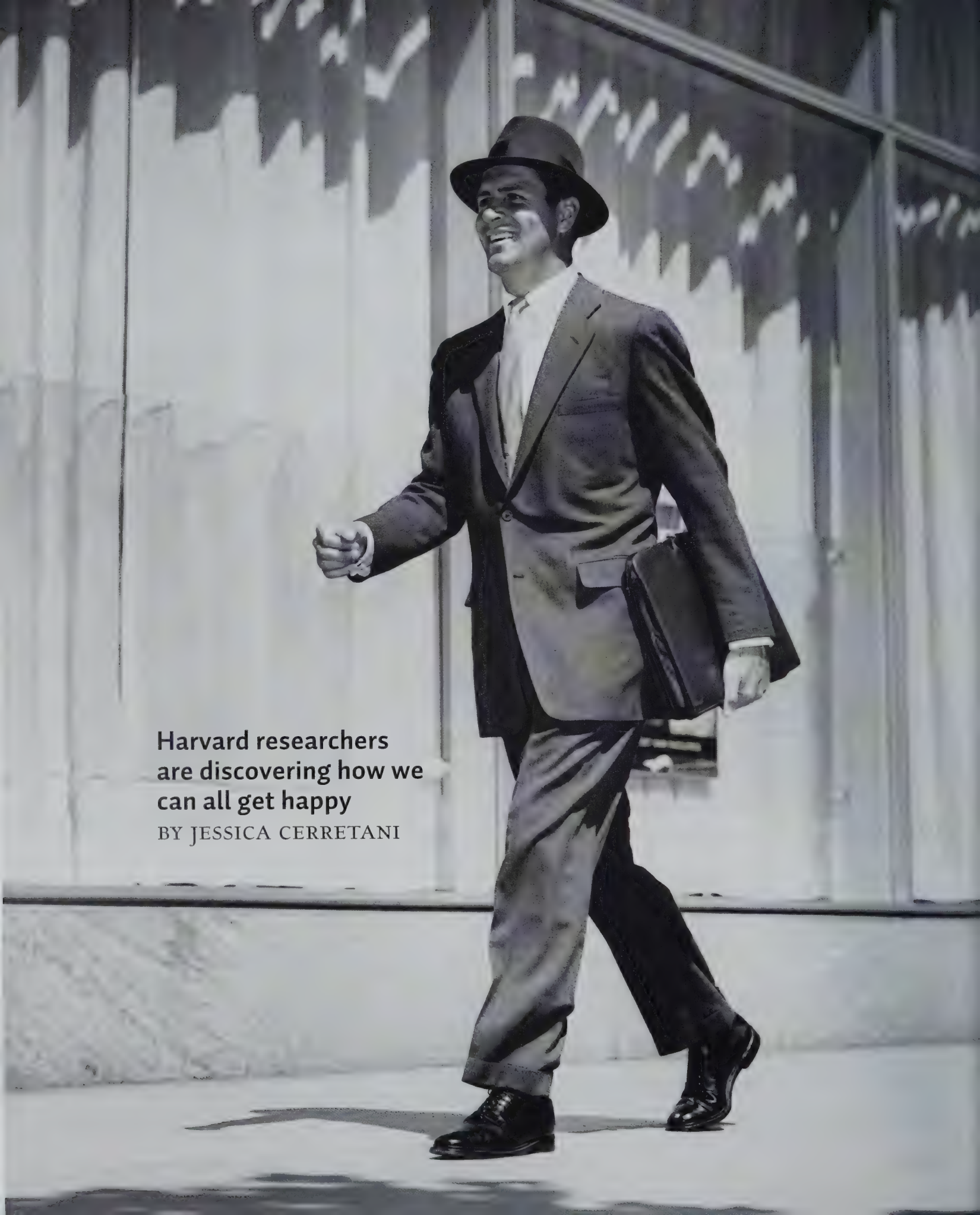
"This is the first time that mechanical force has been implicated in the spread of ovarian cancer," says Brugge, who is also the Louise Foote Pfeiffer Professor of Cell Biology at HMS. "While this research is still preliminary, we are building a foundation for the development of treatments based on a robust understanding of the disease."

The ovaries are located in the peritoneal cavity, whose lining, the peritoneum, is topped with a layer called the mesothelium. After an ovarian tumor develops, clusters of cancer cells are released into the peritoneal cavity. Each cluster floats around until it encounters the lining of the cavity. It attaches to the lining, spreads out, and launches an invasion into the mesothelium. Brugge's team determined how ovarian cancer cells get through the mesothelium to colonize organs on the other side.

The researchers identified three critical players in the invasion process—integrin, talin, and myosin, proteins known to play a role in cell movement. Integrin protrudes from the cancer cells and grabs hold of scaffolding surrounding the mesothelium. Myosin, which is a motor, pulls on integrin through talin. As a result, the cancer cells gain traction and force mesothelial cells out of the way.

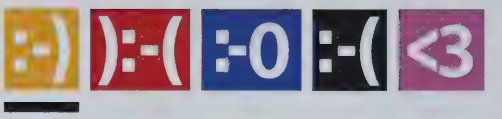
"Eventually, it might be possible to prevent or reverse this invasion process," says Brugge. "We hope that our work will inform such treatments in the future."

—*Joanna Logue*



Harvard researchers are discovering how we can all get happy

BY JESSICA CERRETANI



the contagion of happiness

EVERYONE, IT SEEMS—from Buddhist monks to positive psychologists, from Charles Schulz to the Beatles—has offered opinions on what it means to be happy. And whether you believe that bliss is found with a warm puppy or a warm gun, in a Prozac prescription or the pages of self-help books, you likely crave more of it. For all the bumper-sticker clichés and pop-culture platitudes, though, happiness is one of the less-studied human emotions. It's not a "treatable" problem like sadness, anger, or fear, and its very essence seems more the stuff of greeting cards than hard science. That's changing, however, as a growing number of researchers—including several affiliated with Harvard Medical School—are uncovering surprising facts about the nature of delight.

The Sunny Side

One of the greatest challenges in the study of happiness lies in its definition. "Happiness is a big umbrella term that can mean different things to different people," says Nancy Etcoff, an HMS assistant professor of psychology in Massachusetts General Hospital's Department of Psychiatry. "We can view happiness in at least three ways—as a hedonic state, as a cognitive state, or as a general life philosophy. Happiness, then, can refer to a way of thinking, such as being optimistic; a way of feeling joy, pleasure, relief, or gratitude; or simply a way of being."

Others make a clearer distinction between the concept of happiness and the positive emotions the word describes. "Happiness is just drive reduction," says George Vaillant '59, an HMS professor of psychiatry at Brigham and Women's Hospital who has studied the science of positive emotions. "Let's say you're speeding down the highway and your stomach is growling. You spot the Golden Arches, pull over, and order a Big Mac. That makes you 'happy.'" But that satisfaction is fleeting—the resultant heartburn likely lasts longer than your gratification. Happiness, Vaillant believes, is a conscious state of mind, rooted in the neocortex, the region of the brain responsible for thinking, planning, and decision-making: You eat a hamburger and think, "I feel good."

Joy, on the other hand, is more complex. It's that warm, fuzzy feeling you get when you hear your child's laughter, embrace your sweetheart, or cuddle a puppy. "Joy is all about our connection to others," explains Vaillant. It's a subconscious, almost visceral feeling that appears to stem from the brain's limbic system, which is believed to control emotions, including pleasure. Unlike happiness, joy involves little cognitive awareness—you just feel good without thinking about it—but it's more enduring.

These intricacies have made joy difficult to measure, so scientists tend mainly to tackle what Vaillant calls the "tamer" idea of general happiness in their research. But that, too, has proved tricky. Medicine's penchant for problem-solving means that most researchers have focused their efforts on studying causes of and treatments for gloomier sentiments like sadness, depression, and anxiety. The smiley-faced cheer of happiness seems less serious—and less potentially profitable—in comparison.

Classic studies that compared the emotional well-being of lottery winners, paraplegics, and quadriplegics found all three groups had similar levels of current happiness.

The Pursuit of Happiness

Nevertheless, those who have plumbed the depths of our psyches for more details about how and why we experience positive emotions have uncovered some intriguing facts. Among their findings: Happiness is at least partially genetic. Researchers at the University of Minnesota have found that identical twins appear to share not only the same DNA, but the same general level of happiness, regardless of whether they were raised together or separately. Such studies suggest that nature may play a larger role than nurture in determining our "hedonic setpoint," or happiness thermostat.

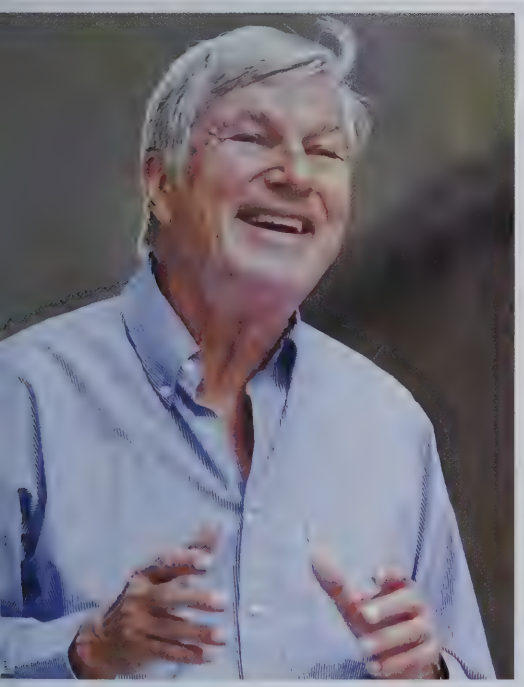
Evolution is also responsible. "Human beings evolved in a dangerous world, where we had to recognize threats to survive," says Etcoff. "As a result, our brains are wired to be much more sensitive to negative emotions and sensations than positive ones."

Perhaps it's this predisposition to pessimism that makes many people wary of looking on the bright side. The exhilarating highs of happiness and joy, after all, increase our vulnerability to the depths of despair—a broken heart, a dashed hope, a shattering disappointment. "Positive emotions," Vaillant points out, "are often associated with tears."

Of course, if you're born with, say, Eeyore's setpoint, that doesn't mean you can't transform yourself into Tigger. While some of us appear biologically prone to shyness, depression, or anxiety, for example, we aren't predestined to a life of negativity. How we find happiness, it seems, may depend on where we look for it—and that isn't necessarily under the plastic

surgeon's knife or in a million-dollar mansion. Although a much-publicized 2011 report from the University of Texas at Austin found that the people ranked most attractive were about 10 percent happier than their less-attractive peers, other research suggests that our own beauty—or lack thereof—has little to do with a sunny disposition. In Etcoff's research for her book *Survival of the Prettiest*, she found that while attractive people tend to enjoy more advantages than plainer people, they don't necessarily experience greater life satisfaction.

Money doesn't always buy happiness, either. A boost in income does appear to trigger an elevation in mood, but only to a certain point—$75,000 a year to be exact, according to one recent study. People with lower incomes—particularly those at or below the poverty line—have more stress, but once financial worries ease, positive emotions plateau. If Bill Gates and Oprah Winfrey are happier than the rest of us, it isn't because of their bank accounts. In the end, a sense of gratitude for what we have may be what



JOY TO THE WORLD: Nancy Etcoff, Nicholas Christakis (above), and George Vaillant have all made research contributions to unlocking the elusive formula for happiness.

heartens us: Classic studies that compared the emotional well-being of lottery winners, paraplegics, and quadriplegics found all three groups had similar levels of current happiness, suggesting that once the initial windfall or trauma fades, we adapt to change and return to our original hedonic setpoint.

Glee Club

So what *does* bring us happiness? Research shows that our relationships with others, rather than what we see in the mirror or find in our wallets, may be what matter most. It's a concept that held true for our cave-dwelling ancestors, who formed elaborate social structures to increase their odds of survival. These days, our connections are more about building a family, gossiping at the water cooler, and adding to our list of Facebook friends than outsmarting saber-toothed tigers. But results of the long-running Grant Study of Adult Development, which Vaillant helps oversee, suggest that the emotional benefits of connectedness remain. Vaillant and his colleagues have found, for instance, that only the capacity for loving relationships predicted life satisfaction in older men.

In turn, being happy can have its own advantages. More than three decades ago, Grant Study data showed that good mental health in men slowed the deterioration of their physical health, even after adjusting for genetics, obesity, and tobacco and alcohol use. Although Vaillant has since found that after age 50 vascular risk factors such as smoking, elevated diastolic blood pressure, diabetes, obesity, and alcohol abuse appear to play a far greater role than mental health in subsequent health and longevity, other research still supports a link to mental health. Research by Ichiro Kawachi, an HMS associate professor of medicine at Brigham and Women's Hospital, found a strong correlation between happiness and good health, both in individuals and within communities.

And there's more good news: Happiness may be limitless. Just as someone's bad mood can rub off on you, positivity, too, may spread, says Nicholas Christakis '88, an HMS professor of medical sociology and of medicine who has researched the contagion of emotions within the larger context of social networks. His findings have shown that happiness may be a collective phenomenon: Having a happy friend who lives within a mile of you, for example, appears to increase the probability that you will be happy as well. In collaboration with James Fowler at the University of California at San Diego, Christakis found similar effects for the spread of happiness between next-door neighbors, siblings that live nearby, and spouses—so that good feelings continue to move from person to person, even when there's no longer a direct connection to the original Pollyanna.

"Just as some diseases are contagious," Christakis says, "we've found that many emotions can pulse through social networks." And unlike the flu, happiness is a gift you can actually enjoy.

Perhaps, as Christakis's research suggests, that's the real key to a rosy outlook.

"Happiness isn't just one big event," Etcoff says, "but the accrual of smaller, incremental steps, such as feeling gratitude and helping others."

Christakis agrees. "Rather than asking how we can get happier, we should be asking how we can increase happiness all around us," he says. "When you make positive changes in your own life, those effects ripple out from you and you can find yourself surrounded by the very thing you fostered." ■

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Scientists probe the nature of wrath in the hope of devising cures

BY ELIZABETH DOUGHERTY

anger management

When Emotional Brakes Fail

Depression and anger often go hand in hand

FLARES AND FLASHES. Outbursts and eruptions. The words used to describe anger tend to be volcanic. And science may explain why. ■ When an angry feeling coincides with aggressive or hostile behavior, it also activates the amygdala, an almond-shaped part of the brain associated with emotions, particularly fear, anxiety, and anger. ■ This finding is one in a series from studies led by Darin Dougherty, an HMS associate professor of psychiatry at Massachusetts General Hospital, that aim to uncover why anger attacks occur in patients with major depressive disorder. Some of these patients experience angry flare-ups that are inappropriate to the situation and out of character for the individual. "People will yell or throw things," says Dougherty. "We wanted to investigate the mechanisms behind those reactions."

For these patients, angry outbursts usually stop when the depression ends. Understanding this link could provide valuable insights into these disorders and their treatment.

Dougherty began in 1999 by investigating healthy people with no signs of depression and no history of angry episodes. He employed positron emission tomography imaging to examine which regions of the brain engage during angry moments. Subjects simulated angry moments by recalling the moments in their lives when they felt rage. "You can try to spark anger by showing upsetting pictures, for example," says Dougherty. "But the response isn't as robust. The best way to induce emotion is through autobiographical scripts."

During angry recollections, the amygdala fired. At the same time, a part of the orbital frontal cortex, just above the eyes, also engaged, putting the brakes on emotion. "Healthy people experience anger," says Dougherty, "but they can suppress it before acting on it."

In depressed people who are prone to anger attacks, this neurological brake fails to engage. In another study, Dougherty found that in people with major depressive disorder and anger attacks the orbital frontal cortex did not activate. Rather, activity in the amygdala increased and angry outbursts ensued. More recently, Dougherty used functional magnetic resonance imaging to achieve a more fine-grained examination of the timing of the amygdala's activation during angry moments.

Now Dougherty is applying these research techniques to examine what happens in the brain during treatment for anger and depression using drugs or cognitive behavioral therapy to better understand how treatments work mechanistically. Ultimately he hopes this work will give clinicians better insights into which treatment options might be best for patients.

THE KIDS ARE NOT ALL RIGHT: Martin Teicher, pictured above, has documented the damage that parental verbal abuse wreaks on the brains of their children.

Sticks and Stones

Verbal abuse injures young brains

EVERYONE FEELS ANGER. Traffic snarls, unsympathetic colleagues, playground bullies; we all have our triggers. The problems start when anger boils over into hostility and aggression, behaviors that cause harm.

According to research from McLean Hospital, seemingly harmless anger may cause invisible damage to the brains of young children. Martin Teicher, an HMS associate professor of psychiatry at McLean, has found that verbal abuse from parents and peers causes changes in developing brains tantamount to scarring that lasts into adulthood.

Teicher began his investigations by examining the effects of sexual abuse, physical abuse, and harsh corporeal punishment on young brains. In 2005, he turned his attention to parental verbal abuse, finding that verbal abuse had deleterious effects on par with witnessing domestic violence and other seemingly more violent forms of maltreatment. In 2009 he used diffusion-tensor magnetic resonance imaging to build an accurate map of the neural connections in the white matter of brains of adults who had experienced parental verbal abuse, but no other forms of abuse, as children.

He found three neural pathways that were disturbed in these adults: the arcuate fasciculus, involved in language processing; part of the cingulum bundle, altered in patients with post-traumatic stress disorder and associated with depression and dissociation; and part of the fornix, linked to anxiety. "The damage," Teicher says, "was on par with that found in the brains of people who had experienced nonfamilial sexual abuse."

More recently, Teicher found that peer verbal abuse—whether teasing, belittling, or disparaging words—can cause similar damage. "Kids often hear many negative things from their peers," he says.

Teicher's latest research suggests that parental and peer verbal abuse may affect children differently throughout development. When experienced during early childhood, verbal abuse can lead to somatization, the translation of emotions into physical illness. During middle school, it can increase the likelihood of drug abuse, anxiety, and depression. In high school, it can lead to increased anger and hostility.

"The expression of a lot of anger can be pathogenic," Teicher says. "Children especially suffer when anger is vented. Openly expressed negative, raw, and intense emotion is hard for many people to witness and can leave scars." That is, children's brains seem to turn down the volume on abusive words, images, and even pain. The result is diminished integrity in these sensory pathways.

Teicher is now investigating the effects of witnessing domestic violence. Early findings suggest that all sensory systems may be vulnerable to violence; abuse that is heard may damage regions distinct from those injured by abuse that is seen or felt. His work as a whole suggests that anger may deserve more attention from psychiatry.

"We've really focused on depression and anxiety as key emotions," he says. "But anger is a big problem. It's a problem when we express it too much and when we express it too little."

In the fifties, people worried that television would turn children into delinquents. Today, parents fear that violent movie scenes and game scenarios will breed anger, aggression, and violence.

The Sound of the Fury

Turn off your phones. And televisions. And game consoles...

EVERYONE, from children to great-grandparents, uses electronic media, and media use will only grow more pervasive. At least, that's how Michael Rich '91, an HMS associate professor of pediatrics at Children's Hospital Boston, sees it.

Yet since the earliest days of television, electronic media has been a blame-taker. In the fifties, people worried that television would turn children into delinquents. Today, parents fear that violent movie scenes and game scenarios will breed anger, aggression, and violence. These accusations against media, Rich believes, come down to values-based arguments, not scientific evidence.

In an effort to drill down to media's true effects, Rich has launched a longitudinal survey study. "We're trying to create the media exposure equivalent of the Framingham Heart Study," he says. The pilot study, now in its third wave of data collection, involves an ethnically and socioeconomically diverse group of 126 middle-school students from Manchester, New Hampshire.

Rich began the investigation with computer-based self-interviews to understand each child's typical media use, health behaviors and health status. For one week, participants carry a Palm Pilot and video camcorder, soon to be replaced by a smartphone, which they are randomly signaled to use during waking hours to capture their locations, companionship, media use, focus of attention, and emotional state. After completing the 58-question form—which, given the media adeptness of the young participants, usually takes less than 90 seconds—participants make a quick 360-degree video of their environment. This video picks up environmental contexts, including media that go unnoticed by participants, such as loud music in the next room, a brother playing a video game in the same room, or even a billboard passing by outside a school bus.


Michael Rich

An early result of the study is the research team's definition of an important new measure: the Media Involvement Index, a measure of overall media immersion. The team's hypothesis is that as children use media devices more frequently and concurrently, the children are more likely to show risks of adverse outcomes. The first findings, published in the February 2011 issue of the *Journal of Adolescent Health*, suggest that children with a higher Media Involvement Index have an increased risk of early alcohol use. Future results will explore how media involvement influences other adolescent health risk behaviors, from smoking to violence.

Rich aims to better understand the ways media affect people's health and intends to share this information through his online parenting column, Ask the Mediatrician. "In a way, urging responsible media consumption is like promoting food safety and traffic safety," he says. "You don't want to lecture people, but to give them facts so they can make informed decisions."

Unlike traditional biofeedback training, in which people learn to calm themselves by disengaging from reality, RAGE Control requires players to stay internally calm during an intense and frustrating activity.

Alien Therapy

A video game trains angry children to keep their cool

PEEW! PEEW PEEW! Missed that alien! Peew! Peew! Oh, no! Just shot a good guy. Peew! Peew peew!

Welcome to RAGE Control (Regulate and Gain Emotional Control), a shoot-'em-up video game designed, as its name suggests, to teach anger management. This counterintuitive game—the kind often blamed for reinforcing behaviors that celebrate anger—works. The key element? When players' heart rates rise, indicating the emotional arousal that can lead to anger, their guns start shooting blanks.

For adolescents who respond to minor stresses with angry and dangerous outbursts, the game may be an alternative to pharmaceutical interventions such as antipsychotics. In addition, says Joseph Gonzalez-Heydrich, an HMS assistant professor of psychiatry at Children's Hospital Boston and leader of the RAGE Control project, the game may enhance the effectiveness of behavioral therapy.

Unlike traditional biofeedback training, in which people learn to calm themselves by disengaging from reality, RAGE Control requires players to stay internally calm during an intense and frustrating activity. In this game, players must destroy googly-eyed aliens falling down the screen without harming the affable snails that squish past.

"We knew this type of game would force the kids to make decisions constantly while still keeping their arousal in check," says Jason Kahn, an HMS instructor in psychiatry who built and helped design the prototype. "Plus it would be something they would *want* to play." The game, modeled after Space Invaders, targets children aged eight and up.

The researchers combine game play with behavioral therapy that teaches such anger management techniques as deep breathing. The game also serves as an icebreaker for therapists. "The game provides patients with an opportunity to talk about their actions and feelings in the context of the game rather than having to revisit uncomfortable, demeaning topics such as past bad behavior," says Peter Ducharme, a clinical social worker at Children's Hospital Boston who is involved in the project. "Practicing the game lets them experience mastering the skills presented in therapy. This in turn allows them to open up about their difficulties."

During the early stage of testing the game, the researchers recruited children who were inpatients in a psychiatric unit. "The alternative treatment for these kids would be antipsychotic drugs, which have a host of side effects and don't get at the root of the problem," says Gonzalez-Heydrich. "You don't learn to control your aggression by taking antipsychotics."

A recent trial of the game compared patients receiving the normal course of treatment with those receiving psychotherapy coupled with game play. Gonzalez-Heydrich cautions that the study was small, and that a larger, randomized controlled trial has started. At the same time, he says, "The game intervention had a profound effect. The kids reported feeling less angry."

Them's Fightin' Words

Serotonin and dopamine drive aggression in fruit flies

RAISED IN ISOLATION, he had no role models. He had never even witnessed a fight. Yet when he stepped into the ring, he had all the moves. He postured, lunged, and boxed, dancing like Muhammad Ali and jabbing like Sugar Ray.

How did he feel when he faced his first foe? Angry? Frightened? It is a question for the ages, for our victorious pugilist is a fruit fly.

"We don't know when flies are angry," says Edward Kravitz, the George Packer Berry Professor of Neurobiology at HMS, who studies fruit-fly aggression. "We can't ask the animals how they feel."

What Kravitz *can* ask, however, is what drives this innate aggressive behavior. Such research, although it does not translate directly to human anger, can provide insights into hostility and bullying. Kravitz saw similar unlearned, unpracticed fighting instincts in lobsters, making the question about hardwired anger even more curious. He selected flies as a model for teasing out the genetics, though, because flies can be bred rapidly and raised in complete isolation.

Kravitz has found that flies show aggressive behaviors when they face competition for resources, such as food or a mate. At first, they all fight the same way, but over time, winners and losers emerge. "Losing flies develop a loser mentality," says Kravitz. They fight less aggressively against opponents they've lost to before and, even though they approach new foes with gusto, they tend to keep losing.

Even bullies, the victors who keep picking fights and winning, will lose their competitive advantage after just one loss.

In recent work, Kravitz bred flies with "tunable" aggression. In these transgenic flies he can selectively turn on and off neurons that contain serotonin and dopamine to determine what roles these neurons play in aggression, fight intensity, and the creation of pecking orders.

Flies show aggressive behaviors when they face competition for resources, such as food or a mate. At first, they all fight the same way, but over time, winners and losers emerge.

Serotonin, he found, is crucial for fight intensity. Without it, flies will not do battle with gusto. Dopamine appears to inhibit aggression: In its absence, flies fight at higher intensity levels. Kravitz and colleagues plan to isolate the specific neurons involved and work out the circuitry that governs these behaviors.

While it's tempting to relate such findings to humans and their mood disorders, Kravitz avoids such equations. "We are after general principles of how these neural circuits work, and some of the chemicals are the same across species," he says. "But the details of the circuitry are going to be completely different."

Elizabeth Dougherty, a former science writer at HMS, is now a freelance science writer and novelist living in central Massachusetts.

COME OUT SWINGING: Edward Kravitz's research team has found that during half-hour fights, fruit flies average 27 encounters of 11 seconds each. The skirmishing flies move so quickly that the researchers need slow-motion instant replay to score them.

Dread requires only a tenth of a second to take root

BY ANN MARIE MENTING

the chill of fear

A COPSE CAN BECKON, with its dappled leaves and songbird trills. But linger past twilight, and tree, bush, and animal assume different dimensions. Trunks thicken and loom, bushes snatch at clothing, and the rustlings and skitters of feather and claw magnify. You become unsettled, unnerved. You *run.* ■ You do this because you're afraid. Even without direct evidence of danger, you're compelled to flee, to protect yourself. Why this compulsion? It's the work of your amygdala, a tiny almond-shaped structure in your brain. Sensory signals alert it; in turn, it triggers a cascade of activity, deluging your body with messages that widen your eyes, prick your ears, accelerate your heart, quicken your breathing, wrench your stomach, moisten your palms, and launch a full-body, organ-clenching, corpuscle-filling chill. You run quite simply because fear grips you. ■ "You could call the amygdala a relevance detector," says Nouchine Hadjikhani, an HMS associate professor of radiology who specializes in capturing the activity of the brain as it reacts to fear-provoking stimuli. "In less than 100 milliseconds, just one-tenth of a second, sensory information reaches the amygdala, which signals your brain to be aware. All your systems become more receptive. You're now ready to fight, freeze, or flee."

TAKING FRIGHT: Mohammed Milad (from left), Nouchine Hadjikhani, Roger Pitman, and Vadim Bolshakov all seek new approaches to fear, which, left unchecked, can have a debilitating effect on people's lives.

The good news is that, should the terror prove benign, you'll not long be in fear's thrall. For while your amygdala is providing survival insurance by spurring action, sensory clues are also traveling to your prefrontal cortex. The amygdala's action buys you additional milliseconds, during which you might glimpse a light, stumble upon a traveled road, or receive other sensory stimuli that your prefrontal cortex will use to temper the initial response. You will calm, completing an arc of reaction that has been key to mammalian survival through eons.

Investigating what drives that arc of reaction spurs much of today's research into the molecular mechanisms of the fear response. HMS scientists are providing tantalizing insights by explaining how we decipher danger in the gazes or body movements of others, by informing treatments for conditions such as post-traumatic stress disorder, and even by providing clues to the gender-based underpinnings of human response to fear.

Fear Factors

A 2005 poll of U.S. teenagers revealed the power that emotion can have in searing fear-filled memories deeply; despite the teens' limited direct experience, terrorist attacks, war, and nuclear war held top-ten berths in a list of fears. This finding hints at a phenomenon that Hadjikhani and her colleagues study: the contagion of fear. In her research, Hadjikhani has found that humans, like other animals, can experience fear indirectly, the result of another's glance or muscle tensing, or, on a larger scale, that electric connection that turns a milling crowd into a stampeding throng.

"We're born into this world with a system to read other people's expressions," says Hadjikhani. "Ten minutes after we're born, we're already oriented more to faces than to objects." In 2008, Hadjikhani and colleagues reported on their investigation of one aspect of facial expression—the gaze—and its role in communicating danger. They found that while a direct gaze from a fear-filled face triggers activity in fear-response regions of the brain, the response is not as complex as that elicited by a fear-filled face in which the eyes are averted. A direct gaze signals an interaction between participants who know themselves to be non-threatening. But an averted gaze, "pointing with the eyes," as the researchers call it, flags a possible environmental danger and sparks activity in brain regions skilled at reading faces, interpreting gazes, processing fear, and detecting motion.

In other research, Hadjikhani found that the brain can recognize happy and fearful expressions in body movements. A fearful posture—hands held open and in front of the body like shields, for example—activates brain regions that oversee emotion, vision, and action, while postures of happiness—arms loosely held from the body as if opened to embrace—spur activity only in vision-processing regions.

These physical communications of actual or perceived danger offer one avenue to developing a conditioned fear, a learned response founded upon emotion and impressed so firmly within memory that it remains active for a lifetime.

Raising the Dread

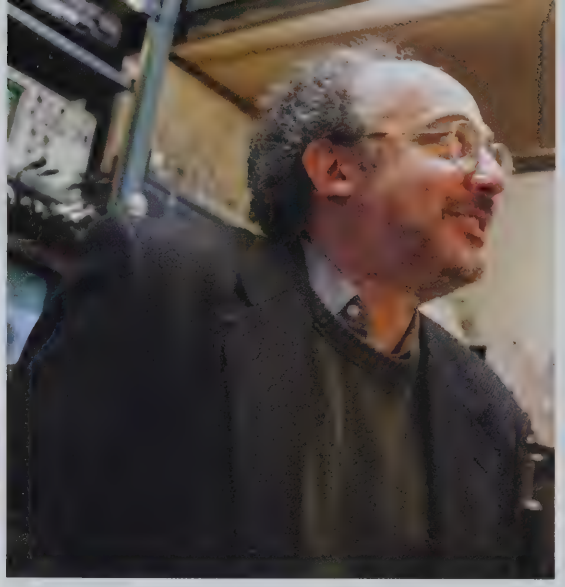
According to the National Institute of Mental Health, roughly 19 million people in the United States have mental illnesses that involve persistent, outsized fear responses to seemingly ordinary stimuli. A door slam becomes a gun's report to a shattered combat veteran, for example, while smoke from burning leaves might trigger smell-based memories of pyres for a genocide survivor. Among the anxiety disorders linked to conditioned fear responses is one that's much in the news: post-traumatic stress disorder.

For more than a decade, Vadim Bolshakov, an HMS associate professor of psychiatry and director of McLean Hospital's Cellular Neurobiology Laboratory, has explored fear-driven disorders by investigating their molecular bases in the brains of rats. One early finding from his laboratory showed that learned fear changes the way the animals' brains operate, offering a mechanism for conditioned fear's persistence.

Bolshakov and colleagues taught rats to associate a harmless stimulus, a tone, with a painful event, a shock to their feet. The researchers found that neurons in the rodent amygdala exhibited remarkable sensitivity to the tone, so much so that the neurons continued to fire after the stimulus was removed. This sensitivity, known as long-term potentiation, is important to memory acquisition. It is normally modulated by glutamate, a chemical that is released into the synaptic spaces between neurons when a message is being passed, but then is deactivated to prevent message over-expression. Bolshakov's team showed that the amygdala's heightened sensitivity was the result of too much glutamate, either because the clean-up process failed or, as the researchers postulated, because production of the chemical went into overdrive.

Other studies by Bolshakov and colleagues identified two proteins essential to the innate and learned fear responses. When the researchers blocked production of one of the proteins, stathmin, fear-conditioned mice were less able to recall the learned fear—and lost the ability to recognize dangers that normally would have kicked their innate fear response into high gear. Blocking the gene that produced a protein known as transient receptor potential channel 5, normally found in high concentrations in the amygdala, decreased the rodents' neurons' sensitivity to cholecystokinin, a neuropeptide released when the innate fear response is triggered or a learned fear is recalled.

These insights are welcomed by Roger Pitman, an HMS professor of psychiatry, and Mohammed Milad, an HMS assistant professor of psychiatry. Based



One way to help patients diminish the impact of an anxiety-producing memory is to guide them to form a new memory that inhibits, or extinguishes, expression of the fearful memory.

at Massachusetts General Hospital, these researchers seek to tease out treatments for people with anxiety disorders such as post-traumatic stress disorder.

Location, Location, Location

"You can never completely abolish a learned fear," says Pitman. "Learned fears are deep and may strengthen by reconsolidating after recall. One way to help patients diminish the impact of an anxiety-producing memory is to guide them to form a new memory that inhibits, or extinguishes, expression of the fearful memory during any recall attempt."

Or, as Pitman and colleagues discovered several years ago, people might be helped to stave off a fear-filled memory by preventing it from consolidating in the first place. In a controlled study of patients entering Mass General's emergency department after traumatic experiences—assaults or car accidents, for example—Pitman provided some participants with a placebo and others with propranolol, a drug that blocks the effects of the hormone adrenaline. At follow-up interviews participants listened to audiotapes of their own accounts of their trauma the day it occurred. Propranolol recipients had weaker physical responses to the tapes than placebo users, who showed physical signs of the stirring of their fearful memory despite time's passage.

Replicating these results has proven difficult, however, so Pitman and colleagues have shifted their focus to reactivating traumatic memories in people with post-traumatic stress disorder and then administering an anti-stress drug to try to weaken the memory's reconsolidation.

Reliving a fear, even a trauma-induced one, is not necessarily pathologic, Milad points out. Recalling the source of high emotion or injury can serve as a safeguard, a warning that our brains can tap as needed. In addition, time often softens the intensity of response.

"Say you're in a car accident," Milad adds. "It occurs at a particular intersection at the same time a certain song is playing on the radio. For a period following that accident, whenever you go through that intersection or hear that song, you will re-experience at some level your initial fear. If over time nothing horrible happens to rekindle your memory, your conditioned response to either stimulus will lessen until the fear is extinguished. This extinction doesn't erase the initial learned fear; instead, it leads to forming a new memory, a 'safety memory.' The learned fear—the neuronal connections that the experience formed within your amygdala and between your amygdala and certain cortical structures—remains."

For some, the trauma never lessens. In people with post-traumatic stress disorder, Milad and Pitman have found that two brain regions involved in extinction, the hippocampus and a region of the prefrontal cortex, function at a lesser capacity, while activity in the amygdala and the dorsal anterior cingulate, a region involved in cognition and motor control, rachets up. These findings may explain the unending rawness that trauma-induced fears bring to people with the disorder.

X Factor

Other research by these investigators suggests that hormones and biological cycles may play significant roles in fear learning and extinction.

"Although some data suggest that estrogen actually enhances fear learning," says Milad, "other studies suggest the opposite, that it reduces fear and anxiety. Unfortunately, the area is underinvestigated. Anxiety disorders, for example, are twice as high in women—and we can't say precisely why."

The researchers' work does provide intriguing clues, however. They have found that women with higher estrogen levels showed stronger activation of the ventromedial prefrontal cortex, a brain region key to fear control. These high-estrogen women were good at extinguishing fear. When the researchers repeated the study in rats and manipulated estrogen levels, they found that blocking estrogen impaired the animals' ability to control fear. Reintroducing estrogen caused the rats to behave as if they felt safe.

Curiously, the researchers found that men's ability to control fear was akin to that of high-estrogen women. How does it jibe, then, that women have twice the prevalence of anxiety disorders?

"We don't know," says Milad, "but the speculation is that estrogen alone doesn't make you a super-extinguisher. It may be the *lack* of the hormone that puts a woman at higher risk. If a woman's estrogen is high, she controls fear in a way comparable to men, but if her estrogen dips, as it would during a normal menstrual cycle, she may be at a higher risk for fear acquisition following a trauma or another emotion-laden incident."

Such studies by Milad and others highlight a growing interest in finely parsing the mechanisms of fear acquisition and extinction in humans. Fundamentally, though, our response to fear remains basic, a primitive emotion essential to our survival and a core response that unifies our species.

"The amygdala is the amygdala," says Milad. "Whether it's in Taipei or in Cedar Rapids, it's still a knee-jerk response to danger."

Ann Marie Menting is associate editor of Harvard Medicine.

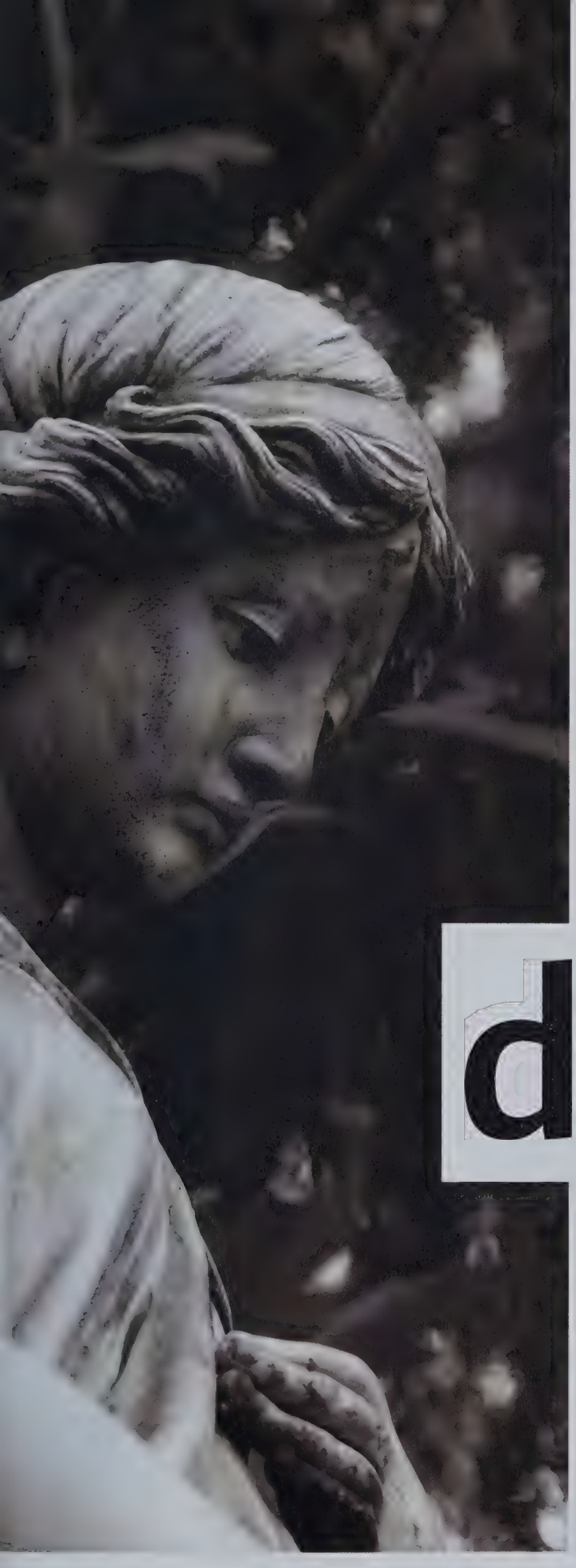


PHOTO: PIXONAUT/ISTOCKPHOTO.COM

Medicine tackles melancholia with new tools and understanding

BY ELIZABETH DOUGHERTY

the depths of despair

Tuning Out Sorrow

Deep-brain stimulation offers hope for depression

Some people with depression have tried everything—behavioral therapy, antidepressants, sleep deprivation, electroconvulsive therapy—to no avail. ■ Now deep-brain stimulation is showing promise for people whose condition is refractory. The therapy, already used in some Parkinson's patients to control tremors, involves implanting electrodes in a region of the brain found to be active during sadness-induction studies.

Darin Dougherty, an HMS associate professor of psychiatry at Massachusetts General Hospital, was principal investigator of a study of five of the world's first fifteen implantations ever attempted to control depression. The procedure, initial studies of which began at Mass General in 2003, involves the surgical insertion of electrodes into the brain's ventral capsule/ventral striatum. After implantation, the physician must tune the electrical stimulation for each patient, after which the device can stimulate the patient's brain continually, even indefinitely. If the device fails, as can happen when the person walks through a theft detector or airport screening device, the depressive symptoms quickly return.

In a follow-up study published by Dougherty and others in a 2009 issue of *Biological Psychiatry*, patients showed response rates of 40 percent after six months and 53 percent after one to four years; those responding showed significant improvement. For a patient to consider such an invasive treatment, their symptoms must be grave. "The degree of illness really highlights the robustness of the treatment," says Dougherty.

A large-scale clinical trial of the technique is now under way, involving more than 200 patients at 20 different sites. Dougherty is hopeful that an interim review of early results by the U.S. Food and Drug Administration will be one more step toward approval of this experimental treatment.

THROWING A LIFELINE. Darin Dougherty has found that deep-brain stimulation can offer hope to those with intractable depression.

Primitive Brains

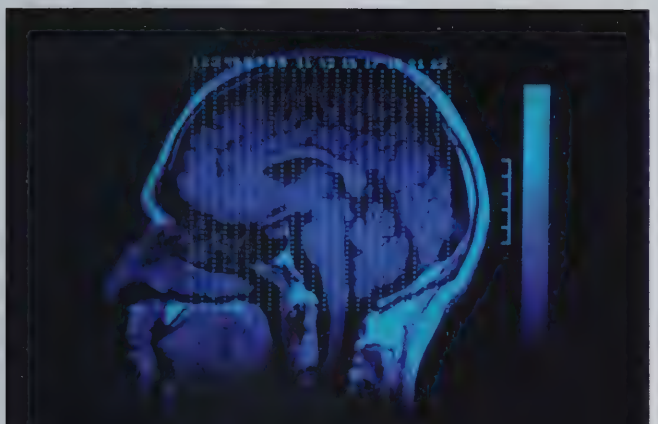
Adults lose their reactivity to sad faces

Is sadness a survival emotion? In 2004, William Killgore, an HMS assistant professor of psychology at McLean Hospital, investigated whether the perception of sadness might be governed by the same unconscious processing as fear or anger. "Our findings indicate that while other emotions have primitive survival value," Killgore says, "sadness appears to be more of a social emotion."

Killgore arrived at this conclusion after investigating whether the subliminal suggestion of sadness triggers activity in the brain's amygdala, a region linked with unconscious, survival-related responses, such as the startle reflex and the fight-or-flight response. In this study, Killgore showed adult participants faces wearing sad expressions. Each sorrowful visage appeared for 20 milliseconds before Killgore masked it with one whose expression was neutral. While viewing the sad faces, participants had no conscious awareness of them, Killgore found. Unlike angry, frightened, and happy expressions, which in earlier research had all produced spikes in amygdala activity, the subliminal sad expressions elicited no such response.

In 2007 Killgore repeated his study with adolescents. These participants showed an unconscious response in the amygdala to sad expressions, suggesting, Killgore says, that young brains may not be ready to distinguish some social emotions from threats. It may be that we learn as we mature to distinguish social cues from primitive survival responses or that we learn to distinguish aroused happy, angry, and frightened faces from subdued, sad ones. Or, Killgore adds, it could be both. He recently found that the amygdala responds in the same way to both happy and frightened expressions, lending support to the arousal hypothesis.

The difference between adults and adolescents does suggest, however, that in youth, "the amygdala is still responsive to a broad range of emotional stimuli," says Killgore. "In adults, the prefrontal region puts the brakes on to better modulate or control responses to social emotions."



Personalized Psychiatry

Researchers hope to be able to predict the success of antidepressants

More than half of clinically depressed patients don't respond to their initial treatment, and weeks often pass before this failure becomes obvious. Each subsequent treatment requires additional weeks to assess. Yet this process needn't be a trial-and-error one, says Diego Pizzagalli, an HMS associate professor of psychiatry at McLean Hospital. Pizzagalli hopes to speed the search for efficacious therapies for depression, not with new medications, but with biomarkers.

"We want to personalize treatment in psychiatry," he says, by giving psychiatrists the tools to find the best path to recovery for each patient. The science is not there yet, he adds, but it may be soon.

A decade ago, Pizzagalli's laboratory discovered that a region of the brain called the rostral anterior cingulate cortex shows elevated activity among people who, though not yet treated for depression, would go on to respond to the treatment months later. This biomarker for elevated activity identified 89 percent of eventual responders; its absence was linked with 89 percent of eventual nonresponders. More than a dozen studies have since replicated this finding.

"The next challenge," Pizzagalli says, "is to find a more treatment-specific predictor." He is part of a group of researchers who recently received funding to do just that. A National Institute of Mental Health grant supports six sites nationally, including McLean Hospital, where Pizzagalli is the principal investigator, and Massachusetts General Hospital. The investigators will recruit 400 patients nationally and collect a range of data, including genetic profiles, clinical symptoms, brain scans using electroencephalography and functional magnetic resonance imaging, and any experience with depression-linked environmental factors, such as stress and early trauma. They will then correlate those data with treatment outcomes.

"We want to see if these data can be combined to derive novel ways for guiding treatments for depression," says Pizzagalli. "We hope to find the next generation of predictors."

UNDER PRESSURE: Randy Auerbach has found that teens who receive little support from their parents and classmates are more likely to be susceptible to stress-triggered depression.

The Path to Sadness

The roots of depression can be uncovered

When it comes to triggering sadness and depression, which comes first, stress or vulnerability? Randy Auerbach, an HMS instructor in psychology at McLean Hospital, suspects it's both.

"The presence of stress isn't enough, and neither is the presence of vulnerability," he says. "It's the interaction of these two risks that converge and pave the path to sadness and depression."

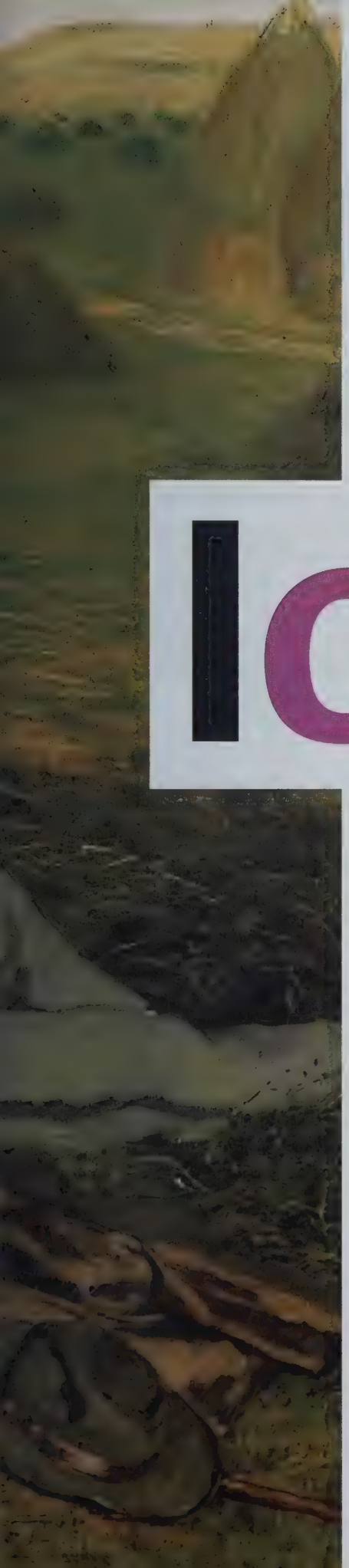
Auerbach's research aims to tease out depression's genesis by studying the interplay of stress with such vulnerabilities as low self-esteem, dysfunctional attitudes, self-referential processing, and a perceived lack of control in the face of adverse events. He focuses on adolescents because 20 percent of people in this age group experience a depressive episode, and most will relapse in adulthood.

Auerbach recently examined the relationship between social support and stress and the development of depression among adolescents. He found that young people with little support from parents and classmates are more likely to experience depressive symptoms in the face of stress. A lack of friends and supportive peers, however, did not contribute to risk for depression. This work appeared in the May 2011 *Journal of Abnormal Child Psychology.*

As a clinician, Auerbach applies his integrated, holistic model by helping patients learn to recognize their feelings, frailties, and susceptibilities so they can move from being reactive to proactive. Someone who feels test anxiety to the point of poor performance, for example, may learn to predict that anxiety, employ relaxation techniques, and interrupt the vicious cycle of stress, avoidance, and impaired function.

"Depression is complex," says Auerbach. "Once we have an understanding of the factors that affect the unfolding of depressive symptoms, we can target them and reduce the despair."

Elizabeth Dougherty, a former science writer at HMS, is now a freelance writer.



PAINTING: "PAIR OF LOVERS," BY PAL SZINYEI MERSE (PHOTO BY ALFREDO DAGLI ORTI/THE ART ARCHIVE/CORBIS)

Love's many splendors begin with empathy and attachment BY DAVID CAMERON

the look of love

WHEN SECOND GRADER Jacqueline Olds arrived home from school one afternoon in 1955, she found the atmosphere charged with excitement. Her parents pointed to a headline on the front page of the *Montreal Star:* "McGill opens vast new research field with brain 'pleasure area' discovery." ■ Olds, now an HMS associate clinical professor of psychiatry at Massachusetts General Hospital, had only vague notions back then of what her father, James Olds, then a postdoctoral researcher at McGill University, did during the day, yet she knew it had something to do with the brains of rats. ■ The elder Olds had just published a paper in the *Journal of Comparative and Physiological Psychology* describing how the rat brain was suffused with desire when a particular region of it was electronically stimulated. The rat would do whatever it could to relive the cerebral voltage regardless of cost, like a jilted lover seeking intimacy anew, or a gambler circling back to the roulette wheel James Olds's discovery of the brain's "pleasure center" has held up for more than half a century, and no scientific discussion on the phenomenon of human love can avoid it. ■ Most of us, even those disciplined to interpret the world through the lens of evidence-based science, can't help but imagine love as a ghost in the machine. St. Paul's famous meditation on the patience and kindess of love, recited in a seemingly nonstop wedding loop, personifies love as an entity embodying what we crave most in others. Love as a spiritual value has so permeated Western culture that even a science-drenched modern fable like the film *Eternal Sunshine of the Spotless Mind* couldn't help but bust it out of its neurophysiologic sheathing. ■ But the scientific evidence is unmistakable: Whatever this thing called love is, we humans need it. Deep attachments to others—and the pleasure-center stimulation those links cause—are as vital to our bodies and minds as food and sleep. Their absence carries catastrophic risk to our health and well-being.

I Feel Your Pain

While many drugs, including antibiotics and certain chemotherapies, gradually lose effectiveness over time, one treatment has manifested a steady rise in potency during the past few decades: the placebo.

Much to the vexation of pharmaceutical companies trying to get antidepressants and pain medications approved for use, clinical trials conducted over the years have revealed the increasing power of the placebo effect. Our efforts to understand that trend throws light on the healing power of doctor/patient connectedness.

Carl Marci '97, an HMS assistant professor of psychiatry at Massachusetts General Hospital, began paying attention to the placebo effect in the early 1990s, while still a medical student. During a course on alternative therapies, he was struck by the amount of time these practitioners of homeopathy, Reiki, and acupuncture spent with their patients.

"Data showed that, with the exception of intense psychotherapy, people were spending far more time each year with alternative practitioners than they were with other health care providers," says Marci. "That got me thinking about the relationship." He began to suspect that the success of these providers had less to do with their therapeutic approach than it did with the time they invested in their patients. He has since spent most of his professional life studying the doctor/patient relationship, using empathy as his framework.

What is empathy, and why does it matter? The term, coined by a contemporary of Freud, goes back to the German word meaning "feeling into." The English novelist Ian McEwan once wrote, "Imagining what it is like to be someone other than yourself is at the core of our humanity. It is the essence of compassion, and it is the beginning of morality."

A slightly more scientific paraphrase might describe empathy as the ability of the brain to accurately mirror the emotions it perceives in another. Marci's contribution to this field is the discovery that most empathy occurs at an unconscious level, evidence that our brains are hardwired for it.

Several years ago Marci conducted a study in which he sought to quantify empathy. Taking 20 patient/therapist pairs, he and colleagues measured the rate at which skin conducted electrical impulses in these subjects, as determined through their sweat production during sessions.

"Skin sweat marks arousal coming from the brain's emotion center, and it accurately measures the depth of emotional response," says Marci. "It can't indicate what you're feeling, but it indicates the depth and the curve, the trajectory, of your emotion."

Marci found that at the moments when the rate of electrical conductivity on the skin of patients and therapists synchronized into matched lines of peaks and gullies, the patients reported feeling most understood. (Interestingly, conductivity was most disjointed precisely at those moments in which the therapists monopolized the conversation.)

Since the mid-1990s, when a group of Italian researchers first proposed the idea of "mirror neurons," researchers have come to grasp that our brains contain dedicated neuronal networks that reflect the world around us. These networks, which reside primarily in the prefrontal cortex—the corner office of cerebral executive function—imitate motions and emotions in a neurobiological monkey see, monkey do. When you witness someone waving, the very part of your brain that activates arm motion and wrist action lights up, even if you jam your hands into your pockets. And despite your efforts to keep your visage impassive, the neurons that animate faces to form beaming smiles flare the nanosecond you glimpse a Cheshire grin. "Our brains are so wired for empathy," Marci says, "that there's zero lag time."

As far as the placebo effect goes, Marci suggests that one explanation for its steady rise is the increasing complexity of clinical trials. The tighter the regulations, the more interactions patients have with a team of providers. The deeper human interaction that presumably results may help explain the increase in the placebo effect.

Which leads us back to the brain's pleasure center, or reward center. Empathy triggers dopamine and serotonin, neurochemicals associated with the reward center's conjoined twin, the brain's emotion center. If, as the scientific literature indicates, mere laughter stimulates the reward center, how much more stimulating would be the act of immersing yourself in the world of another?

When you witness someone waving, the very part of your brain that activates arm motion and wrist action lights up, even if you jam your hands into your pockets.

From an evolutionary perspective, this makes perfect sense. "Human babies have the most postnatal neuronal growth of any species," says Marci. "Without empathy, there is no attachment, and attachment is essential for survival."

Good Chemistry

What happens when empathy is absent? While Marci's model is the doctor/patient relationship, Karlen Lyons-Ruth, an HMS associate professor of psychology at Cambridge Health Alliance, studies the physiological effects of human interactions in a relationship far more primordial: the one between mothers and infants.

Within the field of developmental psychology, Lyons-Ruth is a leading expert on attachment, with a particular focus on attachment gone wrong. "In a sense," she says, "I'm most interested in what happens when love goes awry."

Empathy and mirroring of the infant's states by the parent is a powerful regulator of normal development, says Lyons-Ruth. The biomarker she uses to measure the quality of a mother–infant relationship is cortisol. This steroid hormone has a number of functions, such as increasing blood sugar and helping the body metabolize fats and carbohydrates. It is also

LOVE GURUS: Karlen Lyons-Ruth (from left), Carl Marci, Jacqueline Olds, and Richard Schwartz study the building blocks of love: empathy and attachment.

released in response to stress to help the body mobilize to meet a challenge. Yet too much cortisol can lead to health problems.

Combat soldiers in particular are likely to experience long periods of extreme stress. Such prolonged stress keeps the hormone jacked up, but the human organism's capacity to tolerate such a powerful chemical is limited, so an emergency system clicks in and dams the hormone's flow. This check can result in an individual who goes through life with a blunted stress response system and attenuated emotional engagement.

Normal cortisol levels and stress responses are essential for healthy attachment, says Lyons-Ruth. When a mother's cortisol levels are normal, she acts as an external regulator by being attuned to her baby's fear and discomfort and acting to relieve these negative states. As a result, the baby experiences minimal stress. But when a mother's cortisol response is blunted, her ability to act as an attuned external regulator for the infant may fail.

"We still have much work to do to understand this model of attachment," says Lyons-Ruth. "But our research has shown that mothers whose interactions with their infants are the most disrupted have the lowest cortisol levels." She and her colleague Bjarne Holmes have also observed that the infants of low-cortisol mothers present with low cortisol levels as well. When low-cortisol infants are stressed, though, their cortisol levels fly off the charts. "These babies lack the ability to modulate their stress responses," Lyons-Ruth says. Because antisocial children and adults also show blunted cortisol responses, low cortisol levels among mothers with very young infants set off alarm bells about these babies' future development.

Infants reared in orphanages may be most at risk for blunted stress responses and associated disturbances in their ability to form deep emotional bonds. As Megan Gunnar and her colleagues at the University of Minnesota have shown, many children adopted from orphanages show abnormally low hormone levels similar to those of combat veterans and antisocial adults. But instead of acting antisocial, some of these children exhibit what Lyons-Ruth calls indiscriminate friendliness. They lack the "stranger danger" instinct that is recognized as a healthy component of early development. Indiscriminate behavior often persists throughout childhood, even after adoption into healthy and stable homes.

"The work that Charley Zeanah has done at Tulane is pointing to a possible critical period for the formation of attachment bonds," says Lyons-Ruth. "Despite good care later, unless responsive care is provided before the end of toddlerhood, blunted cortisol and attachment problems can persist."

Lonely Hearts Club

Richard Schwartz has the distinction of being both an HMS associate clinical professor of psychiatry at McLean Hospital *and* the husband of Jacqueline Olds, the psychiatrist whose father discovered the brain's reward center. Together Schwartz and Olds have carved out a niche as experts in the study not only of love and marriage, but of loneliness as well.

They had already written one book on loneliness when a University of Chicago survey found, in 2004, that 24.7 percent of respondents had not spoken to anyone over the prior six months on issues that were important to them. Most striking was that nearly two decades earlier, only 10 percent of respondents taking the survey had reported this circumstance. This finding spurred Schwartz and Olds to tackle a second book on the subject, *The Lonely American.* Their thesis is straightforward: The United States is suffering from a loneliness epidemic, and the feeling is leading to physical and mental stress. "To put it simply," says Schwartz, "loneliness is bad for you."

And there's plenty of evidence to support this notion. In 1988, University of Michigan sociologist James House published a seminal review article in *Science* that detailed a link between loneliness and premature death. Even when circumstances such as accidents were factored out, socially isolated individuals were twice as likely to die within a ten-year period as were non-isolated people.

Maintaining contact with others seems to be hardwired into our biology, such that our bodies become stressed when these connections are threatened. Loneliness, in short, is a form of low-level chronic stress.

"When you're disconnected, your immune system goes to hell," Schwartz observes, citing another landmark study, this one published in *Genome Biology* in 2007 by Steve Cole of the University of California at Los Angeles. In this study, researchers found that chronic loneliness alters the expression of a network of genes associated with inflammation. "If we know that loneliness affects our immune response," Schwartz says, "it's not surprising that it would happen at the level of DNA expression."

As therapists, Schwartz and Olds constantly encounter patients who suffer from chronic loneliness, yet most are hesitant to label it as such. As diagnoses go, depression and anxiety are less embarrassing. But it's hard to overestimate the psychic pain that loneliness can cause. Think of the nibbling feelings you had as a child (or an adult!) when you suspected you were being purposely left out. Then try to imagine the pain of ostracism or, taken to extremes, the outright torture of solitary confinement.

"Few higher mammals are solitary," observes Schwartz. "Humans are relatively helpless as individuals in the natural world. Part of what makes us so powerful is that we've banded together in small groups. And part of the pain of loneliness is the recognition that without other people we simply can't survive."

Nor surprisingly, loneliness and substance abuse often go hand in hand. "Many drugs, particularly stimulants, trigger the dopaminergic reward center," Olds says. "But we now know that social connectedness and the feeling of being loved also activate that same reward center. If you lack the relationships needed to stimulate that part of your brain, you'll likely find it in a drug."

Blanche DuBois's legendary line in *A Streetcar Named Desire*, "I have always depended on the kindness of strangers," is evolutionarily and neurologically true. Empathy and attachment are at the core of human relatedness, and a small section of our prefrontal cortex drives us to find it one way or another. Without it, we're lost.

"Attachment to others," says Olds, "is the original reward." ■

David Cameron is the director of science communications at Harvard Medical School.

Plight

of the Living Dead

What can science fiction teach us about science fact?

BY JESSICA CERRETANI

Undead Reckoning

The man lurches. Hunger pangs rack his body no matter how much, or how often, he eats. His skin, a sickly grayish green, reeks of decay. And whatever ails him seems to be catching. The diagnosis: Ataxic Neurodegenerative Satiety Deficiency Syndrome, or ANSDS. The patient is a zombie.

The undead, one hopes, are confined to celluloid. But for Steven Schlozman, an HMS assistant professor of psychiatry, zombies play a critical, if fanciful, role in his work, both in and out of the classroom. The monsters serve as a teaching tool for basic neurology—for what the undead can teach us about the living. They also help ensure a captive audience.

"When I walk into a room to give a lecture, people see a short, bald, bespectacled guy who's there to talk about psychiatry, and they assume my class will be boring," Schlozman says. "Then I start talking about zombies, or *Buffy the Vampire Slayer*, or another pop-culture reference, and they're hooked."

Schlozman has long been a horror film aficionado, but his interest in what makes zombies tick was piqued by a real-life scare. Late one night several years ago, while searching for a diversion from the stress and worry of his wife's struggle with breast cancer, the psychiatrist found himself absorbed in a favorite flick, *Night of the Living Dead*. But this time, George Romero's 1968 classic wasn't just a flight of escapism for Schlozman.

"I found myself thinking that if I ever ran across anyone who displayed all the symptoms of a typical zombie, my first instinct wouldn't be to shoot him, but to take him to the emergency room," he says. "I began to wonder what, as a physician, I'd want to know about that person's health."

That curiosity kicked off a tongue-in-cheek quest to diagnose zombie signs and symptoms. He noted three main clues: zombies are slow, they move awkwardly, and their only goal-oriented behavior is to try to quell a constant craving for human flesh. Drawing on a physician's knowledge of basic neurology, Schlozman related these traits to specific regions of the brain known to control certain motor functions.

That unsteady plod? It could be the result of dysfunction in the cerebellum and basal ganglia, the areas responsible for fluid, coordinated movement. The ataxia

THE GHOUL CAN'T HELP IT: If you should ever encounter Night of the Living Dead zombie Karen Cooper, don't try to bash her skull in; simply rush her to the nearest hospital.

attributed to the undead, Schlozman points out, resembles the totter of people with Parkinson's disease, which also affects the basal ganglia. That yen for a meal of *braaaiiiins*? A problem in that same organ's satiety center, the ventromedial hypothalamus. All this damage, Schlozman theorizes, may mean that zombies are almost completely ruled by the amygdala, that primitive, reptilian part of the brain responsible for basic emotions. In that sense, the undead resemble the amygdala-driven crocodile.

Diagnosing the undead to explain brain basics is the whimsical premise of Schlozman's recently published novel, *The Zombie Autopsies*. The real power of the psychiatrist's fascination, however, may lie in what these silver screen villains have to teach us about ourselves.

"Romero-type zombies move so slowly you could eat a sandwich waiting for them to attack you," says Schlozman. "Yet in every movie, we're overcome by throngs of these creatures. I wanted to know why." The answer, he suspects, lies in mirror neurons, nerve cells that scientists believe "light up" not only when we do something, but when we observe another person perform that same action. The mirror-neuron response is what makes us flinch when we see someone get hurt and what makes a monkey start peeling a banana when he sees his simian pal do the same. In other words, mirror neurons appear to be responsible for empathy.

When confronted by zombies, which look like—and well might be—decomposing versions of our friends and neighbors, those mirror neurons kick in. "Zombies still appear somewhat human," Schlozman says. "We hesitate to believe that they're harmful until it's almost too late; then we give ourselves permission to bash their brains in and cheer about it." Ultimately, though, our celebration is hollow, because the undead just keep lurching along—not out of hostility, but out of hunger. "You can blow up only so many zombies," Schlozman says, "without losing your own humanity."

Schlozman's lighthearted theories have struck a chord with his colleagues. He's led grand rounds and given lectures on zombie neurology at Brigham and Women's Hospital, the University of Texas, and the American Psychiatric Association, and he has even roped his coworkers at Massachusetts General Hospital in on the fun.

"The head of our transplant infectious disease service rolled his eyes when I first explained what I was doing," Schlozman says. "But at one o'clock the next morning, he sent an email full of suggestions for what might trigger a zombie outbreak." (For the record, cinematic zombie blooms seem to be prompted by whatever we find most frightening at the moment: nuclear radiation, prion diseases, deadly strains of influenza.)

For Schlozman, whose work in child and adolescent psychiatry can be stressful, scary movies serve to relieve anxiety. And his hobby has workplace applications: it helps his students learn. "There's nothing in the canon that says we shouldn't use celluloid monsters as a way to teach," he says. "Medicine can be hard work—there's no reason we can't all have a laugh now and then."

Scientists could engineer an elephant genome so it resembles that of the woolly mammoth, or modify it slightly to obtain key mammoth characteristics, such as thick, shaggy hair or a swooping tusk.

SUSPENDED ANIMATION: With its DNA dating back some 65 million years, beyond the reach of genomic sequencing, the *Tyrannosaurus rex* must depend on keyboard strokes for his resurrection. When it was released in 1993, *Jurassic Park* became a landmark in the use of computer-generated imagery.

Bring Out Your Dead

Two terrified children cower in a Jeep as a *Tyrannosaurus rex* stalks them, the result of an eccentric billionaire's whim gone horribly awry. The film, of course, is *Jurassic Park*, the blockbuster based on the bestselling novel by the late Michael Crichton '69. In this tale, scientists use DNA from fossilized mosquitoes to clone dinosaurs and other prehistoric creatures, which they house in a futuristic theme park. But could such a flight of fancy become reality? "It's not a matter of *if*," says George Church, an HMS professor of genetics, "but *when*."

The buzz about resurrecting ancient species began in earnest in 2008, when Pennsylvania State University researchers announced that they had a first draft of the complete genetic sequence for the woolly mammoth, the first deciphering of an extinct species' genetic code. Their success was rooted in their approach. Although previous attempts to extract the creature's DNA from fossilized bones—which often harbor bacteria and other contaminants—had failed, the Penn State researchers used frozen tufts of mammoth hair extracted from the Siberian permafrost to recover genetic material. Soon scientists and the media alike were suggesting that the unlocked DNA could someday be used to recreate the mammoth—essentially breathing new life into a creature long relegated to the past. The recent sequencing of the Neanderthal genome—by a team that included David Reich, an HMS professor of genetics—has heightened the debate about the plausibility and ethics of cloning extinct species, whether animal or human.

"The ability to recreate animals from their DNA is a skill set we should have," says Church, who helped initiate both the Human Genome Project and the Personal Genome Project. "Access to this information could help us reestablish certain species if they were destroyed in a disaster, for example." The best way to recreate a woolly mammoth, for instance, might be to create an embryo with the found DNA, then implant it into an elephant, a cousin to the mammoth. But other options exist, Church notes. Scientists could engineer an elephant genome so it resembles that of the mammoth, or modify it slightly to obtain key mammoth characteristics, such as thick, shaggy hair or a swooping tusk.

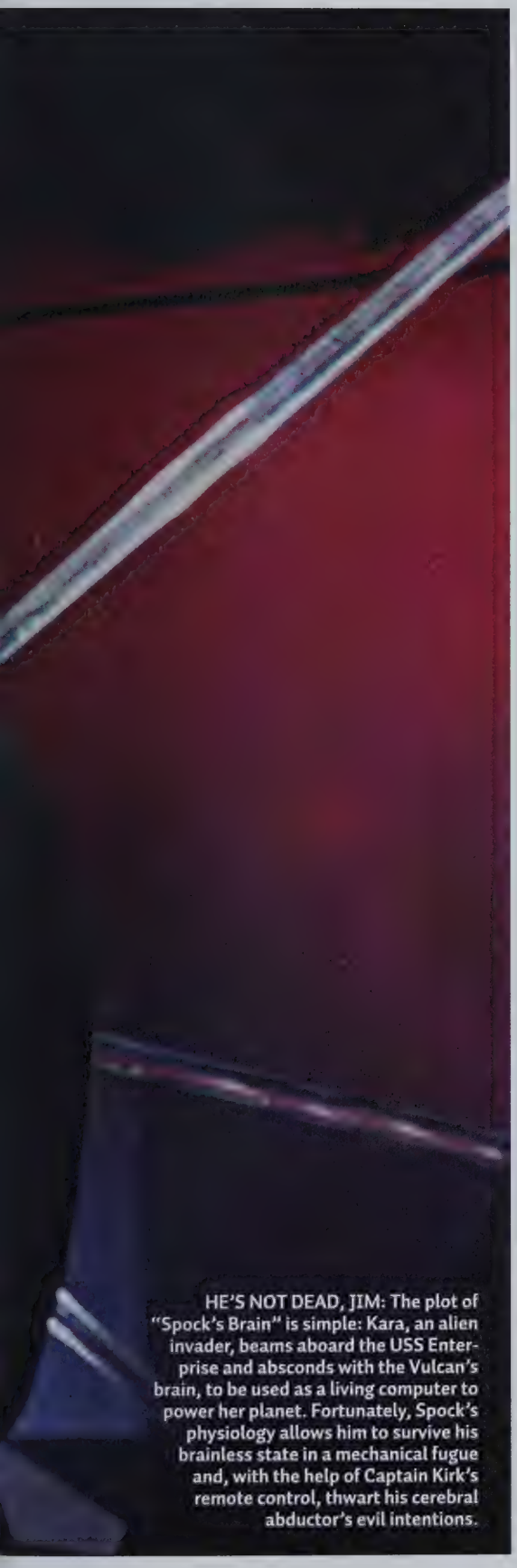
As Crichton's tale warns, such a venture carries both undeniable benefits and unsettling risks. Environmental experts point out that in certain parts of the world—Siberia, for example—the disappearance of mega-fauna such as the woolly mammoth, which foraged in these areas, has led to a diminished ecosystem. The problem? "You can't just transplant an Indian elephant or other existing animal into Siberia," says Church. "It wouldn't survive." But a woolly mammoth, pure or hybrid, might thrive there—and so, in turn, be able to resurrect the surrounding environment. And a cloned Neanderthal, Church adds, could teach us much about medicine, health, and human behavior.

On the other hand, the introduction of smaller animals that are more difficult to manage could result in invasive species—those that reproduce quickly, crowd out or threaten native creatures, and leave viruses or other harmful agents in their wake.

Then, of course, there's the ethical dilemma. At what point, critics wonder, does a scientific endeavor devolve into folly for our own amusement? Imagine the implications of a real-life Jurassic Park in which cloned woolly mammoths, other prehistoric beasts, or worse, Neanderthals, exist solely to entertain humans.

For now, it's an intriguing yet hypothetical concern. Church predicts that, with enough study, cloning could become as socially acceptable and commonplace as other once controversial procedures, such as blood donation and in vitro fertilization. More important, he believes, is the need to focus on what we can do now to preserve biodiversity.

"We should be doing all we can to save species from extinction in the first place," he says. What shouldn't we expect? *Triceratops* and *Velociraptors* stomping through our neighborhoods. Although scientists may soon be able to sequence the genome of any creature that became trapped in permafrost during the past 100,000 years, that omits the time of dinosaurs. The future, it seems, is less *Jurassic Park* and more *Ice Age*.



HE'S NOT DEAD, JIM: The plot of "Spock's Brain" is simple: Kara, an alien invader, beams aboard the USS Enterprise and absconds with the Vulcan's brain, to be used as a living computer to power her planet. Fortunately, Spock's physiology allows him to survive his brainless state in a mechanical fugue and, with the help of Captain Kirk's remote control, thwart his cerebral abductor's evil intentions.

PHOTO: PARAMOUNT PICTURES/GETTY IMAGES

Brain Drain

Any science fiction fan worth his or her tricorder is familiar with "Spock's Brain." In that classic *Star Trek* episode, a comely alien beams aboard the USS *Enterprise*, incapacitates the crew, and absconds with the logical Vulcan's brain. Captain Kirk, Dr. McCoy, and the rest of Spock's cohorts have just 24 hours to locate the organ and return it to its owner's cranium. From its portrait of meddlesome extraterrestrial women to its portrayal of Spock's "reverse brain transplant," the episode is B-movie cheesiness at its best.

For Jeffrey Macklis '84, however, "Spock's Brain" isn't just an amusing take on 1960s Hollywood's vision of the future. Although he's no Trekkie himself, the HMS professor of neurology and of surgery at Massachusetts General Hospital and director of the MGH–HMS Center for Nervous System Repair uses the episode to teach students and clinicians just how far our understanding of neuroscience has advanced.

"'Spock's Brain' is a playful way," he says, "to raise the idea that brain and spinal cord repair are no longer just the stuff of science fiction."

Research findings out of Macklis's laboratory have helped make such a statement possible. Long considered infeasible, the repair of damaged or degenerated corticospinal circuitry has moved from fantasy to fact within the past three decades. Now research by Macklis and others suggests that, with the right combination of molecular signals, it's possible to induce neurogenesis—the birth of new neurons—in mice. That discovery could someday help slow the ravages of the neurodegenerative disease amyotrophic lateral sclerosis, or ALS, and help people with spinal cord injuries recover movement.

While he hesitates to assign a timeframe to a progression from mice to humans, Macklis believes that neurogenesis could make the transition from bench to bedside relatively soon. "This won't happen in just a few years, but translating these findings to humans won't take centuries, either," he says. "We might be able to start using these approaches to improve the health of people with spinal cord injuries or ALS within the coming decades."

Many people may find this concept stunning, but Macklis feels it can be explained by blending heavy science with light fiction. In presentations intended to teach medical students and practicing physicians about neurogenesis, he weaves in the melodramatic plotlines of *Star Trek*, the 1962 flick *The Brain That Wouldn't Die*, and other science-fiction offerings. In one screenshot from "Spock's Brain," Dr. McCoy dons a spiky clear-plastic helmet to communicate with Spock's missing organ. "Here we have one of the first examples of a wireless Internet device," chuckles Macklis. In another screenshot, the crew surrounds Spock after the delicate surgery has reunited him with his gray matter. "This," Macklis says, "is the first recorded brain transplant."

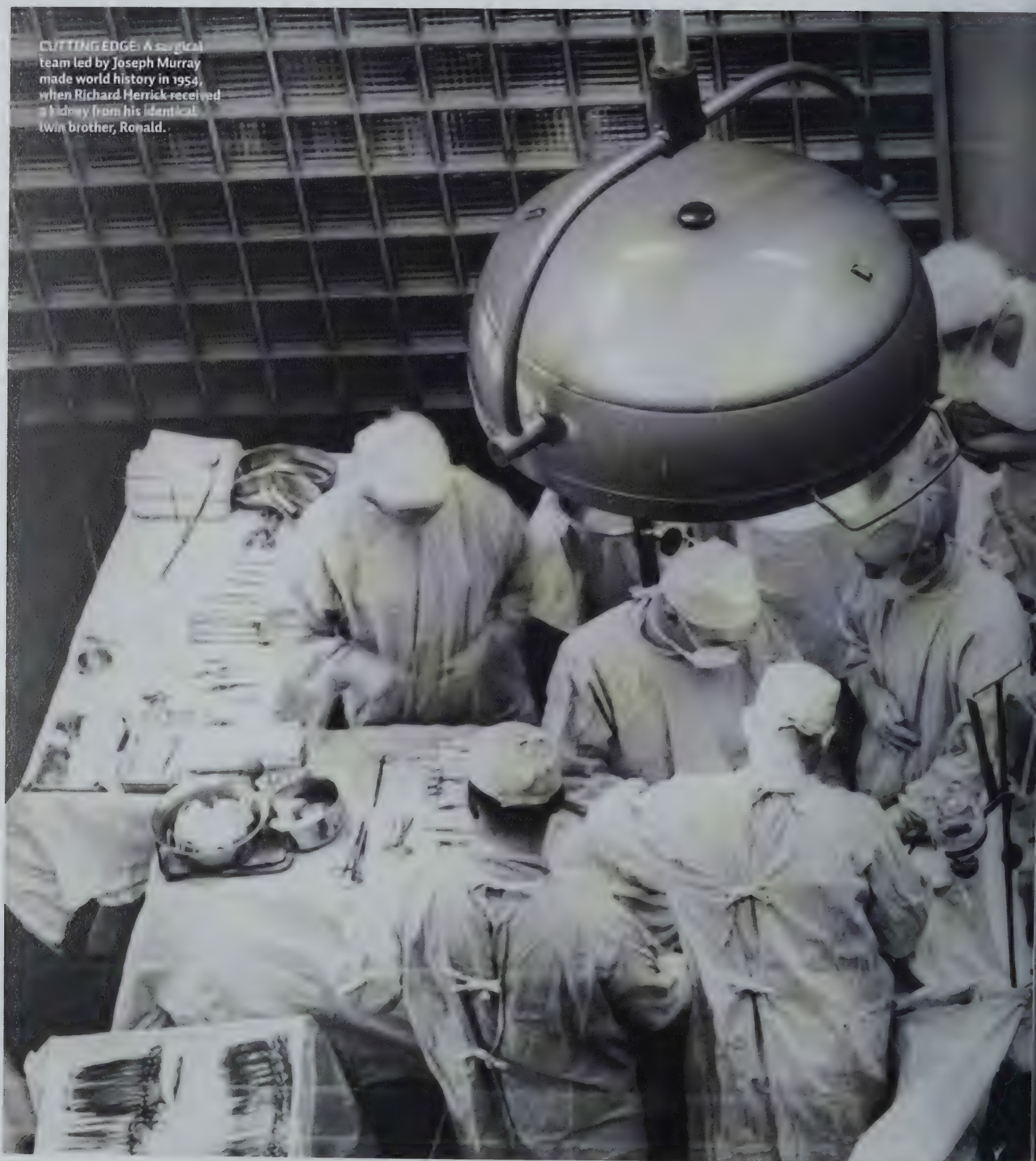
Macklis's pedagogical approach is effective. "Many people learn best through storytelling," he says. "That's what I'm doing here. Students tend to be familiar with *Star Trek*, and these stories, interwoven with hard data, help them understand the concepts."

Science fiction plays another, less obvious role in Macklis's work. When he began assembling his laboratory in 1993, induced neurogenesis was considered an unattainable goal. Yet the neuroscientist believed that, with the right tools, it could be achieved.

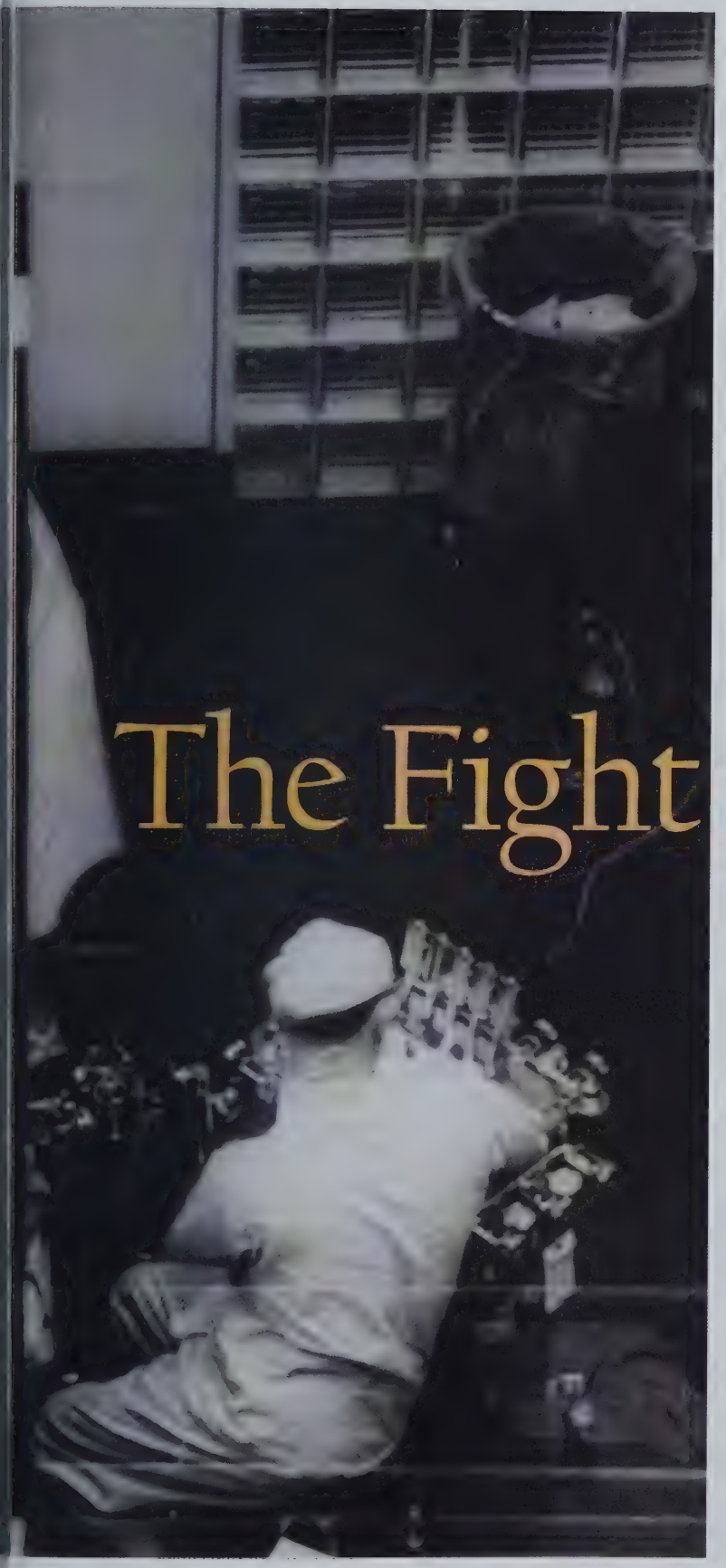
"I drafted a 30-year plan for my lab," he explains. "I knew I'd need tools that didn't yet exist, so I had to predict what other investigators might develop in those three decades and what resources might become available to us."

His approach doesn't differ so much from that of science fiction writers, who create fictional futuristic worlds based on best guesses. "My greatest career satisfaction is that what we once considered impossible is now within reach," Macklis says. "We've progressed from being told we were crazy to even imagine activating and directing neurogenesis, to watching graduate students discover how to generate mouse neurons in the lab on an ordinary Tuesday afternoon." It's research, he hopes, that will someday help us all live long—and prosper. ■

Jessica Cerretani, a former assistant editor of Harvard Medicine, *is now a freelance writer.*



CUTTING EDGE: A surgical team led by Joseph Murray made world history in 1954, when Richard Herrick received a kidney from his identical twin brother, Ronald.



The Fight for Life

The pioneering surgeon of the world's first successful human organ transplant reflects on the gift of life

BY JOSEPH E. MURRAY

THE WORLD'S FIRST successful transplant of an internal organ from one living person to another took place on December 23, 1954, at the Peter Bent Brigham Hospital, in Boston. By a remarkable coincidence, though, the story began for me exactly ten years earlier. ■ On that day, December 23, 1944, a 22-year-old airman, Charles Woods, met with a devastating accident. Woods was assigned to fly the "Hump" over the Himalayas—from Kurmitola, India, to Lüliang, China—ferrying fuel to the Flying Tigers of the Chinese Army, who were fighting the Japanese. An error by Woods's copilot caused their plane to explode on takeoff. The fire caused third-degree burns over 70 percent of Woods's body, and it erased his face. No one had ever recovered from such massive burns. Lacking functional skin, Woods was prey to severe fluid loss, infection, shock, and death.

BOND OF BROTHERS: Richard (left) and Ronald Herrick leave Peter Bent Brigham Hospital less than a month after the historical kidney transplant. Richard lived for eight years after receiving his brother's donation; Ronald died last December in Augusta, Maine, at the age of 79.

I was the junior member of a U.S. Army surgical team charged with saving Woods's life. Our only hope was to drape on him the skin of another soldier who had died—to "transplant" skin from one human to another. Since Woods's immune system would reject this skin as foreign, our probability of success was low. Fortunately, the foreign skin was not rejected as swiftly as we had feared; the trauma and resulting malnutrition had slowed the airman's immune response. This delay, coupled with his remarkable will to live, allowed him to slowly regenerate his own skin, sparing him from death.

Our next challenges were to recraft Woods's face and to create hands that might allow him to again pilot a plane one day. Over nearly two years, we performed 24 operations. Taking skin from other parts of his body, we rebuilt his nose, ears, eyelids, and lips as best we could, and we gave him functional hands. Still, Woods looked nothing like the person he had been and, likely, resembled no one you have ever seen. When we had done all we could, Woods looked in the mirror, walked out into the world, married, raised a family, began flying again, built a successful business, and lived another 58 years.

Thus, in one of my earliest experiences as a surgeon, I had reconstructed a badly damaged face and had taken an organ—in this case, skin—from one person and transplanted it to another. Although I did not know it then,

Miller started to explain that a transplant wouldn't work because Richard's body would reject his brother's kidney, but the doctor stopped mid-sentence. Richard and Ronald, he suddenly remembered, were identical twins.

TWIN CITIES: Joseph Murray holds the torch as he and Ronald Herrick attend the U.S. Transplant Games in Minneapolis in 2004. Above, Ronald Herrick shows Barbara Fisk, a nurse at Boston's Peter Bent Brigham Hospital, a photo of his brother in Coast Guard uniform.

those two themes would come to dominate my professional life. Half a century later, I would watch as others fused the two themes into one with the advent of face transplantation—but I'm getting ahead of the story.

I returned from the war to the Brigham and Harvard Medical School, recruited by the brilliant young chairmen of the departments of surgery and medicine—Francis Moore '39 and George Thorn—to help them pursue a radical dream. Moore and Thorn were determined to cure chronic kidney failure, a disease that, at that time, was a death sentence. Another young recruit, John Merrill '42, had modified a dialysis machine that could temporarily filter the blood in place of kidneys that had stopped working; back then, though, dialysis could not provide long-term support for kidneys that had permanently shut down. Moore and Thorn were convinced that kidney transplantation could be a viable treatment for permanent kidney failure, and they wanted me to be part of a team to turn their dream into a reality.

It was a daunting challenge. First, we had to figure out the human anatomy. Although Alexis Carrel had described vascular suturing in the early 1900s, we had to figure out the best location in the abdomen to hook up the new kidney's blood vessels to the patient's own. Nerves posed another problem: Once the tiny slips of nerves that ran through the kidneys were severed, they could not all be reconnected. Then there were the lymphatics. Would a new, transplanted kidney need to be hooked up to a person's lymph system in order to remain alive? No one knew.

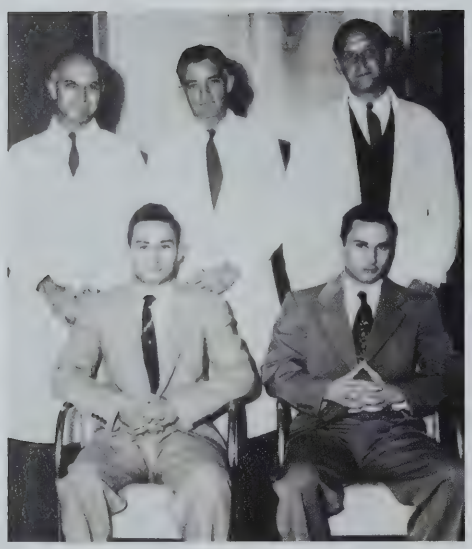
The anatomical hurdles were low, however, compared to the immunological one: How could a transplanted organ avoid rejection? Before human organ transplantation could take a first step, we had to solve the immunological challenge—or render it moot. In October 1954, fate rendered it moot.

Fighting Chance

In the fall of 1953, while serving a tour of duty on a Coast Guard vessel in the Great Lakes, Richard Herrick fell ill. The 22-year old's kidneys were inexplicably failing. Herrick was told that this condition was incurable and that he had two years to live. By August 1954, he could barely walk.

Richard's distraught brother, Ronald, met with Richard's private physician, David Miller. Ronald said he would do anything to help his brother. When told there was nothing anyone could do, Ronald persisted. "Doctor, I'd give him one of my own kidneys if it would help," he said. Miller started to explain that a transplant wouldn't work because Richard's body would reject his brother's kidney, but the doctor stopped mid sentence. Richard and Ronald, he suddenly remembered, were identical twins.

By a stroke of luck, Miller knew about our transplant program. On October 26, 1954, Richard was transferred to the Peter Bent Brigham Hospital. He was gaunt and white from severe anemia. Uremia had affected his brain, making him a difficult patient, disoriented and combative. He cursed the medical staff and accused them of sexually assaulting him. He bit a nurse who was trying to change his sheets. He pulled



THE RIGHT STUFF: The Peter Bent Brigham Hospital transplant team included (back row, from left): Joseph Murray, surgeon for the recipient; nephrologist John Merrill, a team co-leader and a former editor of this magazine; and J. Hartwell Harrison, surgeon for the donor. Right: Joseph Murray holds his Nobel Prize certificate.

out his intravenous lines and catheters. In short, he was a handful. If Richard had anything to say about it, we would not give him treatment of any kind—let alone place another person's kidney into his belly.

As for Ronald, his offhand comment to Miller about donating a kidney had triggered a cascade of events, but did he really understand what his offer entailed? For that matter, did we? The kidneys are vital organs. Do we really need the two we are born with, or is the second just an insurance policy? Actuarial tables at the time suggested that living with one kidney carried no increased risk, but the data were weak.

Moreover, the surgical procedure needed to remove Ronald's kidney contained undeniable risks—complications from general anesthesia, hemorrhage, accidental injury of a nearby vital organ, infection. This list of potential risks posed an ethical dilemma for us. While we routinely asked patients to incur some risk in order to achieve a benefit for themselves, none of us had ever asked a healthy person to accept this magnitude of risk solely for the sake of someone else.

We consulted with experienced physicians within and outside of the Brigham, clergy of all denominations, and legal counsel before offering the option of transplantation. The team met several times with the family to describe in detail what was involved for Ronald and Richard. We advised neither for nor against the operation, and we stated the obvious: *We could not know if it would work.*

Ronald and the family wrestled with unanswerable questions. "It was shocking to me even to consider the idea of giving up my kidney," Ronald told me after the operation. "I felt a real conflict of emotions. Of course, I wanted to help my brother, but the only operation I'd ever had was an appendectomy, and I hadn't much liked that." Ultimately, the decision was settled for Ronald by the undeniable fact that his kidney was his brother's only hope. Once Ronald had made up his mind, there was no turning back. Richard, though, wasn't so sure. In a lucid moment on the eve of the operation, Richard sent an urgent note to Ronald's hospital room: "Get out of here and go home!" Ronald wrote in reply, "I am here, and I am going to stay."

Several days before the operations were scheduled, the press became aware of what was about to happen. Suddenly, the whole world was watching. The media quoted doctors who said the experiment was not only doomed to failure but also unethical. Those of us on the surgical team began to understand what it felt like to be a pitcher in the World Series. The difference was that, unlike that pitcher, we were about to attempt something we had never done before.

While we routinely asked patients to incur some risk in order to achieve a benefit for themselves, none of us had ever asked a healthy person to accept this magnitude of risk solely for the sake of someone else.

The operations began at 8:15 on the morning of December 23. My team opened Richard's abdomen and isolated the main blood vessels we would attach to the new kidney, ready to cut them the moment the new kidney arrived. In the next room, a team led by J. Hartwell Harrison '33 was operating on Ronald, ready to remove one of his kidneys the moment I gave the signal. The twins lay 50 yards apart, Ronald under general

SIBLING REVELRY: Richard (left) and Ronald Herrick celebrate their successful surgeries.

anesthesia and Richard sedated and under continuous spinal anesthesia.

When everything was ready, I took a deep breath and gave Harrison the go-ahead. Timing was critical: From the moment we disconnected Ronald's kidney from its blood supply to the moment we attached it to Richard's circulatory system, the kidney would be without oxygen and nutrients. The longer the interruption, the greater the chance that Ronald's kidney would sustain damage—and thus fail to keep Richard alive.

We started connecting Ronald's kidney to Richard's blood vessels at 10:10 a.m. and finished one hour and 22 minutes later. Had we taken too long? As we removed the clamps on the vessels and Richard's blood began to flow into his new organ, the operating room fell silent. We watched—some with fingers crossed, some saying silent prayers—as the transplanted kidney gradually turned pink and plumped up, engorged by Richard's blood. Then urine began flowing briskly. There were grins all around. Two hours later, Richard and Ronald were in the recovery room, slowly awakening from anesthesia.

Both Richard and Ronald recovered smoothly. Ronald's single kidney was doing the job of two, and Richard's new kidney was more than compensating for his two diseased ones. Richard's improvement was stunning. Within a week, his erratic behavior disappeared. His appetite sharpened, his pallor gave way to his normally ruddy complexion, and his energy level returned. Richard left the hospital after two weeks and continued a courtship he had begun with a nurse who had cared for him in the recovery room. They subsequently married and had two children.

Throughout the next few years, our team at the Brigham performed several more successful kidney transplantations on identical twins. We also began to transplant kidneys between people who were not genetically identical, using various techniques to fight tissue rejection. Although we had several successes, for eight years most of our efforts ended in failure. People who were destined to die young, died young anyway, despite our best efforts. While our colleagues sometimes judged us harshly, our patients and their families did not. They understood that our treatment might well fail but that they had no other hope.

Fortunately, major discoveries in immunology and pharmacology by a pantheon of doctors and scientists—including Robert Schwartz, William Dameshek '23, George Hitchings, and Gertrude Elion—led to drugs that stifled tissue rejection without unacceptable toxicity. Other surgeons—Jean Hamburger, René Küss, Roy Calne, and Thomas Starzl, to name a few—also made important contributions to the techniques for transplanting kidneys. Still others pioneered the transplantation of other organs.

In the late 1960s, I left the field of organ transplantation and spent the rest of my surgical career repairing faces, and other parts of the head and neck, that had been damaged by injury or disease, as well as faces that bore congenital deformities. By 1986, when I retired from surgery, organ transplantation and facial reconstructive surgery had become separate and distinct fields.

Then, on November 27, 2005, those fields fused. Jean-Michel Dubernard, who had once worked at our HMS surgical research laboratory, performed the world's first partial face transplant in Amiens, France, on a woman whose face had been destroyed during a dog attack. Face transplantation has since been performed successfully elsewhere, including in a program at Brigham and Women's that began in 2009.

Grace and Favor

In the summer of 2004, I attended the U.S. Transplant Games in Minneapolis. More than 2,000 participants competed in most of the Olympic sports. Their families and other spectators nearly filled that city's Metrodome.

Workers at the National Kidney Foundation, the sponsor of the games, uncovered remarkable stories about some of the participants. Will Smith was on Team Maine. Smith was a trainer who, some years before, had helped a client, Ellen Souviney, shed 55 pounds, become an athlete, and regain her self-esteem. Smith then developed kidney failure and became terribly ill. Every member of his family was tested, but none was genetically similar enough to donate a kidney. Hearing of Smith's plight, Souviney had herself tested and turned out to be a match. She gave Smith her kidney. At the games, Smith won three medals in track.

Robert Gooch was a healthy preschooler who contracted hepatitis and developed liver failure. Neither parent was a good genetic match, but an uncle was, and he gave part of his liver to the boy. Following surgery, Robert lay in a coma for several days, but gradually he recovered. He won two medals in swimming.

Ronald Herrick, then 73, and I, then 85, were invited to light the torch. We stood on a platform high above the playing field. Below us were throngs of competitors—jumping, stretching, loosening up. The new organs within them had allowed them not only to remain alive, but also to compete.

I thought back to the day when it all began. Ronald and I were still here, but Richard and the rest of our team were gone. So too were many of the recipients—including all those who died young despite our best efforts. They had all understood, perhaps better than we, that life is precious and fragile, and often must be fought for. They went to their graves believing that if they were not going to make it, they might at least help us learn how to save someone else. Their fight, their courage, gave the gift of life to millions.

Many of the donors were gone as well, but some of the remarkable gifts they had given remained alive. How I wished that all of them—donors, recipients, doctors, nurses, scientists—could be standing there with us on the platform, watching the competitors playing on that sunny field of green. ■

Joseph E. Murray '43B, a professor of surgery emeritus at Harvard Medical School, was awarded the Nobel Prize in Physiology or Medicine in 1990. A more complete story of human organ transplantation can be found in his autobiography, Surgery of the Soul *(Science History Publications/USA, 2001). Anthony L. Komaroff, with whom he collaborated on the book and this article, is the Simcox-Clifford-Higby Professor of Medicine at Harvard Medical School and editor-in-chief of Harvard Health Publications.*

ASSEMBLY INSTRUCTIONS

HOW TO BUILD A BETTER VACCINE

Polio, diphtheria, measles, smallpox. Each a scourge through the ages; each now preventable because of a vaccine. Medical science has scored considerable successes in developing these guardians of health, saving millions of lives each year. For every vanquished pathogen, though, many more lurk.

The challenges for vaccinologists are enormous. The ideal vaccine keeps resistance high for a long time, preferably a lifetime. It is safe and free of side effects, effective as a single dose, stable, and affordable, even for vulnerable populations in the developing world. Clearing this high bar may seem impossible, especially when the time factor is considered: Vaccines often require a decade to develop and an additional decade to test for safety and efficacy.

For more than 200 years, ever since Edward Jenner famously used cowpox to inoculate a boy against smallpox, vaccines have relied on pathogens that are alive yet weakened or "killed." But according to Darren Higgins, an HMS professor of microbiology and immunobiology, advances in laboratory technologies—combined with breakthroughs in such fields as genetics—are shaving years off discovery. And new ways of thinking about testing vaccines promise to save time without sacrificing purpose. Here Higgins outlines key steps to building better vaccines for new adversaries.

—Ann Marie Menting

1 Unmask your foe.

First things first: Determine why people are getting sick. Perhaps a noxious chemical is causing harm, or an environmental agent is triggering cancer. To finger an infectious cause, you must scrutinize symptoms. Do they appear in nearly everyone who has fallen ill? If an agent is infectious, how might it be spreading?

2 Divide and conquer.

To help nail down the cause, collect samples for analysis. Blood, sputum, and even the revisited remains of a semi-digested meal may hold a clue to the causative agent. Staining blood samples can bring to light bacteria and even break them into classes that might respond to antibiotics. Vaccinologists are increasingly turning to polymerase chain reaction, or PCR, a technique that zeroes in on genetics—and can pare months, even a year, off the search for a pathogen.

3 Locate next of kin.

Study the PCR and DNA sequence analysis for familiar features. The malefactor responsible for the recent SARS outbreak, for example, was found to be genetically related to coronaviruses, for which an effective antiviral existed. Is there a gene you can silence, thereby undoing the disease agent? If the relatives are bad but not deadly, a vaccine may not be the answer. Rhinoviruses go unchallenged in part because colds are tolerable. But for potentially deadly influenza viruses, vaccines are reformulated annually.

4 Build your armor.

Ponder for a moment the merits of vaccine type: therapeutic or preventive? Preventive vaccines have tended to rule. All childhood immunizations are designed to block their respective disease; vaccines for adults are, too. But the new wave is the therapeutic vaccine, one that boosts the immune system to lessen symptoms, such as the vaccine being developed for herpes simplex virus type 2. If the agent uses a toxin to cause disease, you can deactivate it and spur immunity with a toxoid vaccine.

5 Choose your weapon.

More is better: Vaccines that stimulate both arms of the adaptive immune system—B and T cells—represent the new ideal for vaccinologists. Conjugate vaccines are one example. Certain subunits trigger antibody production by stimulating B cells, white blood cells that recognize foreign invaders. Other subunits spur helper-T cells and their killer cousins to recognize and eliminate pathogen-infected cells. Genetic insights into the interloper can direct or update subunit formulations and may one day allow physicians to customize vaccines to suit pathogen and patient.

ILLUSTRATION: WESLEY BEDROSIAN

Smart Brain Aids

Harvard researchers are finding new ways to help take a load off our minds

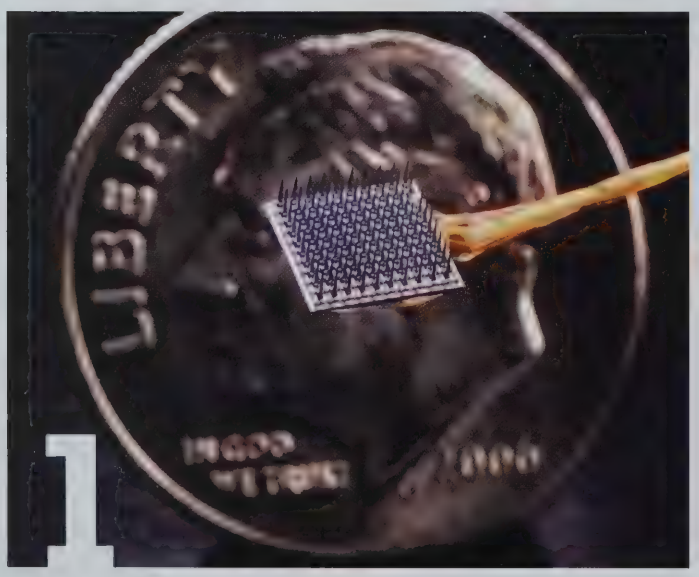
1 Telepathic Therapy

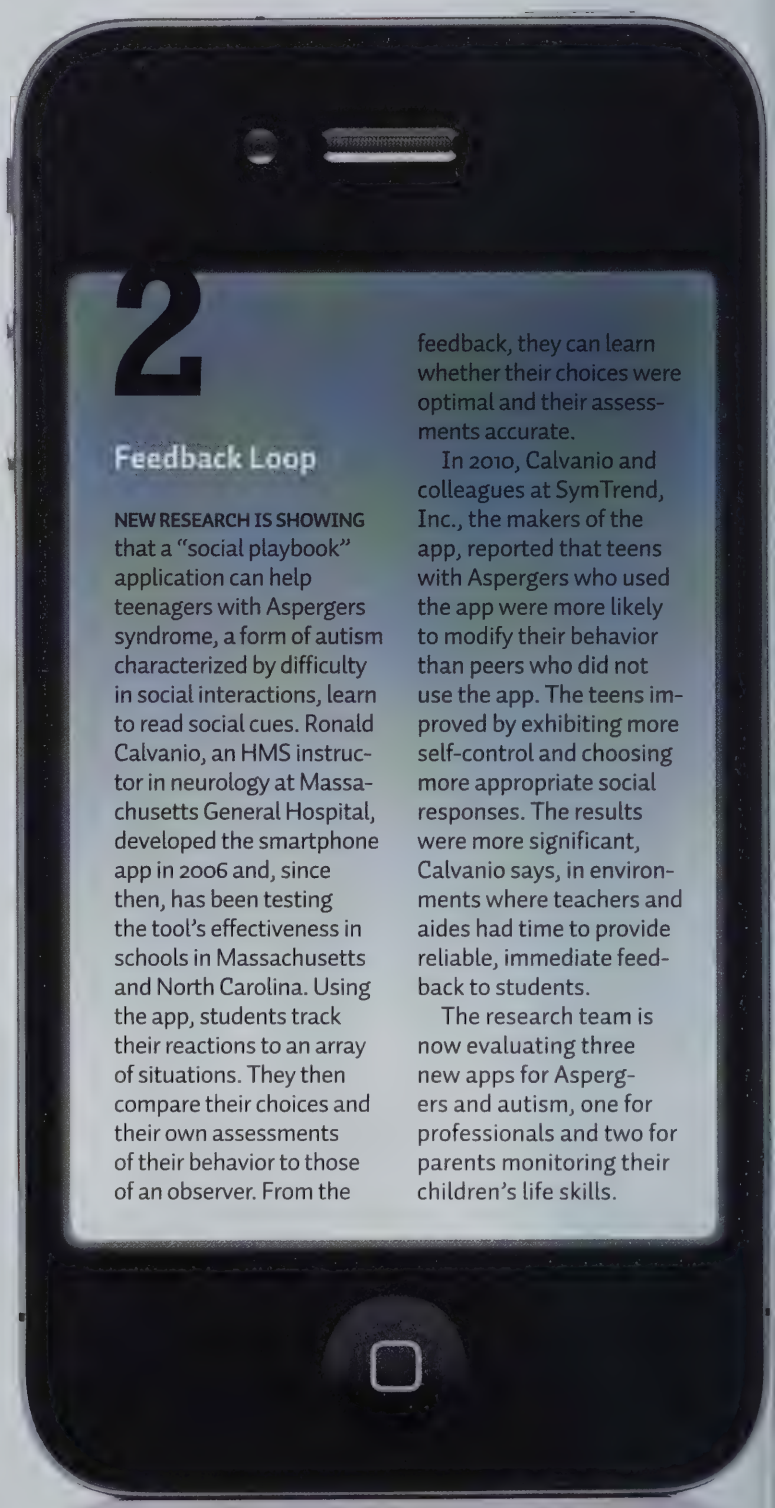
A BRAIN IMPLANT the size of a baby aspirin may soon change the lives of people with quadriplegia. The device, a four-millimeter square array of microelectrodes, sits inside the brain, where it records imagined arm and hand movements and transmits those neural signals to an external computer bank. The computers then translate the cortical imaginings into directions that guide a cursor on a computer screen.

Dubbed BrainGate, the prototype device has logged more than a thousand days of continuous performance in the brain of a paralyzed woman. The patient has maneuvered a cursor on a computer screen to perform point-and-click tasks with 90-percent accuracy and to hit targets the size of a typical computer menu icon.

This is a welcome milestone, says Leigh Hochberg, one of BrainGate's principal investigators and an HMS visiting associate professor of neurology at Massachusetts General Hospital."While there is still a lot of research to do, long-held hopes for chronic intracortical recording technologies are becoming a reality. This research is providing a glimpse into what might be possible."

The research team has already demonstrated simple robotic limb, prosthetic hand, and wheelchair control through BrainGate2. Hochberg is now directing a feasibility study of the technology. The ongoing clinical trial, which will enroll up to 15 patients, is testing safety and examining whether patients might use the device for more complex tasks, such as operating an email program.





2 Feedback Loop

NEW RESEARCH IS SHOWING that a "social playbook" application can help teenagers with Aspergers syndrome, a form of autism characterized by difficulty in social interactions, learn to read social cues. Ronald Calvanio, an HMS instructor in neurology at Massachusetts General Hospital, developed the smartphone app in 2006 and, since then, has been testing the tool's effectiveness in schools in Massachusetts and North Carolina. Using the app, students track their reactions to an array of situations. They then compare their choices and their own assessments of their behavior to those of an observer. From the feedback, they can learn whether their choices were optimal and their assessments accurate.

In 2010, Calvanio and colleagues at SymTrend, Inc., the makers of the app, reported that teens with Aspergers who used the app were more likely to modify their behavior than peers who did not use the app. The teens improved by exhibiting more self-control and choosing more appropriate social responses. The results were more significant, Calvanio says, in environments where teachers and aides had time to provide reliable, immediate feedback to students.

The research team is now evaluating three new apps for Aspergers and autism, one for professionals and two for parents monitoring their children's life skills.

Special Spyware for the Brain

EYE DROP OR BRAIN BIOPSY? Someday soon, those could be choices to the same end. Philip Liu, an HMS associate professor of radiology at Massachusetts General Hospital, has developed a gene-detecting brain probe that can be administered using a simple eye drop.

The technology consists of a standard MRI probe—a tiny substance, just 30 nanometers in diameter, detectable using magnetic resonance imaging—attached to a DNA strand. When administered, the solution flows from the eye through the blood–brain barrier and into brain cells. It binds only in cells with similar strands of messenger RNA, allowing selective targeting and magnetic resonance imaging of genetic activity.

The probe has proved effective in mice with leaky blood–brain barriers. In mice without such leaks, Liu has delivered the drug using a blood–brain barrier bypass similar to cortical and lumbar punctures.

The technology is based on the premise that specific gene activity in brain cells plays a role in cancer, neurodegenerative diseases, drug addiction, and mental health. Liu's noninvasive probe could be tuned to detect specific forms of cancer, brain changes that might indicate Alzheimer's or Parkinson's disease, or stem cell activity.

"We hope to bring expertise in molecular biology into medicine without relying on biopsies," says Liu, who is working to expand the technology's applications.

Help Yourself

WHILE ADVANCED TECHNOLOGIES are helping people get the most out of their brains, sometimes the best medicine doesn't involve technology at all. According to research at Massachusetts General Hospital, meditation is a fast and technology-free way to make positive brain changes. One study followed 16 people enrolled in a meditation course in which participants practiced "mindfulness," paying attention to the present moment with acceptance and curiosity rather than ruminating about the past or agonizing about the future.

After an eight-week session that included 30 minutes of daily meditation, participants showed significant brain changes. MRI scans revealed gray matter density growth in the left hippocampus, the posterior cingulate cortex, the temporoparietal junction, and the cerebellum, brain regions that are involved in learning, memory, emotional regulation, and perspective taking. A similar earlier study showed decreases in amygdala gray matter density that correlated with reduced feelings of stress.

"When people report feeling better after they meditate, it's not just a subjective account," says the research team leader Sara Lazar, an HMS instructor in psychology. "The data show that there's a biological reason why they're feeling less stress."

—Elizabeth Dougherty

FIVE QUESTIONS

KEITH LILLEMOE ON THE FUTURE OF THE SUTURE

Let's look back to the future. Where were the frontiers of surgery at the start of your career?

Cardiac surgery was nearing its peak, and pancreatic surgery was a bit of a backwater; you didn't see great outcomes, so many surgeons avoided it. But advances, particularly at Johns Hopkins and Massachusetts General hospitals, made the operation safer and left cancer patients with better results. We were able to make a lot of progress with pancreatic cancer over two decades, and it felt great to be part of that. That's what stimulated my interest in pancreatic surgery.

Where are the comparable frontiers today?

The frontiers today lie in advancing procedures even further, to refine minimally invasive techniques. Seven years ago, people never imagined that the Whipple procedure or liver resections could be done laparoscopically, and now they are. Other frontiers lie in the areas of organ replacement and regeneration, either through transplantation or—what's even more exciting—through efforts to build new organs from tissues and cells that are being engineered into functioning organs. Some are skeptical that these advances can be made, but people—including many at Massachusetts General Hospital and Harvard Medical School—are working to make it happen.

What's the biggest hurdle?

Technology. Many new techniques require special levels of instrumentation and access that are still in development—robots, for example. Not everyone agrees that these techniques are worth the expense or even necessary. We need to be able to show that they're as safe and effective as surgery done in an open fashion. Many of these operations still carry the risk of significant, sometimes even life-threatening, complications. When a safe open procedure is an option, we can't introduce a technique that compromises patient safety just for the sake of being minimally invasive.

Keith Lillemoe, MD
Surgeon-in-Chief
Massachusetts General Hospital

Keith Lillemoe, a leader in pancreatic and biliary surgery, became chief of the Department of Surgery at Massachusetts General Hospital in April 2011.

So how do we know when newer is better?

The best way to prove anything in medicine is through a randomized controlled trial. But that's much harder with procedures than with, say, medications. Usually you're trying something that you believe is better, and neither patients nor surgeons are willing to say, "I'll take the old procedure, even though I believe the new one is safer." So we compare our new results with our old results. We do an operation the new way 20 times, and then compare the results with those of 20 operations we did the old way. That's good evidence, but it's not the highest level of evidence. As a result, many new procedures never have supportive evidence that reaches the highest rung on that ladder.

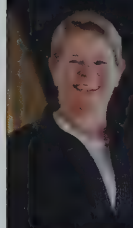
What do you see as the future of surgical training?

Challenges in training residents include limitations on the hours they can work and the complexity of procedures. Hospitals are discharging patients faster, so residents have limited exposure to preoperative and postoperative care. How can we train residents to be efficient, so teaching doesn't slow down a case or extend the duration of an operation? It's called simulation. If residents can use simulation to refine their hand–eye coordination and learn surgical procedures before they enter an operating room, they'll be better for it, and so will patients. We need to find a way for trainees to practice surgical techniques in a non-pressured, simulated environment, where they're not hurting anybody or wasting time, but learning the steps they'll need to take to ensure safe and successful operations.

—R. Alan Leo

PHOTO: JOHN SOARES

President's Report



During the new academic year, the Alumni Council will explore two themes in depth: the continuity of idealism and the culture of innovation. Idealism and innovation represent the best of the Harvard spirit, but they are qualities easily lost in today's challenging health care environment. The Council will learn more about the longitudinal third-year health care experiences that Cambridge Health Alliance pioneered and other Harvard hospitals launched, followed by medical schools around the world. This longitudinal experience has been shown to enhance rather than sap the innate idealism of third-year students. We will also look at the best models for innovation in medical education. We welcome input from alumni on these new initiatives.

Finally, the Alumni Council salutes Paula Byron for her dozen years as editor of this magazine and congratulates her on her new position at Virginia Tech. Her touch with *Harvard Medicine* will be sorely missed. She is a force hard, if not impossible, to replicate.

Phyllis I. Gardner '76 is a professor of medicine at Stanford University School of Medicine.

RE-FORMING CARE: Harvey Fineberg spoke of the effects of persistent increases in health care costs.

STAND AND DELIVER

Tackling the health care delivery crisis

This year's alumni symposium tackled a dilemma familiar to all—the Crisis in Health Care Delivery—or the "perpetual crisis," as symposium moderator Harvey Fineberg '71 called it. Speakers described reform efforts at various levels.

Fineberg, president of the Institute of Medicine, pointed out that in the 1970s, health care expenditures were bewailed as having "soared" to 6 percent of the gross domestic product; now they are close to 18 percent. "We need to deliver the care that American people deserve and the U.S. can afford," said Fineberg.

Until this past spring, Richard Frank, the Margaret T. Morris Professor of Health Care Policy at HMS, was on leave as deputy assistant secretary for policy and evaluation in the U.S. Department of Health and Human Services, which is charged with implementing much of the Patient Protection and Affordable Care Act. Implementation challenges, he said, include answering such questions as which health benefits are essential, how much price and benefit negotiation should be done by insurance exchanges rather than consumers, and how delivery should be organized and costs addressed through accountable care organizations. "Over the next 10 to 15 years," Frank said, "we can expect to cover 34 million new people out of the 50 million now uninsured."

JudyAnn Bigby '78, secretary of health and human services for Massachusetts, countered some of the myths of the state's health care reform. Far from a failure, she said, only 1.9 percent of Massachusetts' citizens remain without health care insurance. Rather than breaking the state budget, the reforms added only about 1 percent to total state spending per year. High on the agenda is cost containment, however, which the state is trying to approach through such means as posting cost and quality-of-care data, addressing malpractice, and reforming how health care is paid for by better integrating and coordinating services and by avoiding unnecessary care. "Our system is obsolete," Bigby said, "and we need to change it."

Other countries get more value from their health care systems by spending less, and primary care is a key component of that success, said Russell Phillips, chief of the Division of General Medicine and Primary care at Beth Israel Deaconess Medical Center and interim co-director of the HMS Center for Primary Care. Data show, he said, that as the concentration of primary care physicians rises, so does quality, and in states with more primary care physicians, the cost of care drops. Intent on being a leader to spur interest and innovation in this specialty, HMS founded the center last October.

To watch a video of the symposium—and to view videos and slide shows of other Alumni Week events—visit alumni.hms.harvard.edu/events/2011-reunions.html.

—Ellen Barlow

PHOTOS, FROM LEFT: GARY PARKER; JUSTIN IDE/HARVARD NEWS OFFICE

CLASS NOTES

NEWS FROM ALUMNI

1945

Giulio D'Angio

"I was amazed to learn that the Children's Hospital of Philadelphia named me the Richard D. Wood Sr. Distinguished Alumnus, given that I trained at the Boston Children's Hospital under Robert Gross and Martin Wittenborg."

1946

Charles Carothers

"The Carothers family includes five generations of orthopedists, a legacy that began in the early 1900s. I am retired, my son Thomas is in orthopedic practice in Cincinnati, and grandson Josh Carothers practices in Albuquerque."

1947

Armand D. Versaci

"I received an honorary doctorate in the humanities from the Catholic University of Nicaragua in 2010. I also received the faculty Alpha Omega Alpha Award in April 2011, from the Alpert Medical School of Brown University."

1948

Robert Zullo

was honored with the Bishop's Award from Saint Peter's Healthcare System in April 2011 for his nearly 60 years of service to Saint Peter's, the system's mission, and the community of New Brunswick, New Jersey.

1949

Francis Riley

"Marion, my dear wife for 41 years, died on March 3, 2011, after a protracted, complex illness."

1952

Wesley Byerly

"I recently went to Durgapur, India, to work in an Anglican Church children's compound. I stopped in Vietnam for one week to see where I had been in 1967 and 1969–70. Then on around the world."

James Donovan

"I'm still doing well physically and battled the last Maine winter to another standstill. I lost a brother, Thomas Donovan '46, this year. Best to all the '52ers."

Warren Guntheroth

"I'm still working, and now have 334 publications. My wife of 53 years, Ellie, died in 2007. I'm feeling much better now that Sally, a classmate of Ellie's, is with me."

1955

John Laszlo

"We continue to stay busy with travel, national park visits, and senior university courses. We're enjoying our four children and four grandchildren. Pat and I are taking our family to a dude ranch in the Smokies for my 80th. Saddle up! Best to my classmates!"

1956

John Grover

"Philippa and I, newly settled in Chula Vista, California, did not make the class reunion. Sorry to have missed it—regards to all."

1957

William Greenough

"I attended the 50th anniversary celebration of the Cholera Research Lab, now the International Centre for Diarrhoeal Diseases Research, Bangladesh. It was particularly memorable as I admitted the first cholera patient in November 1962 and directed the research center from 1979 to 1982."

Mark Kartchner

"I have made multiple voluntary surgical missions to Bolivia and Nicaragua over the past ten years by way of repaying society for the outstanding education HMS afforded me to further my career."

Victor Sidel

"This fall, Oxford University Press will publish the second edition of my book *Terrorism and Public Health: A Balanced Approach to Strengthening Systems and Protecting People*."

1959

Norman Clemens

"Julie and I were privileged to share in moving tributes to **Charlie Epstein** at a shiva service in February. He will be sorely missed by his family, friends, congregation, and the profession in which he was a leader."

1961

Mark Hanschka

"I'm doing well! My health is excellent. I'm busy with community efforts and visits to children and grandchildren."

Newton Hyslop, Jr.

"In October 2010, I was pleasantly surprised to receive the Spirit of Charity Award from the Medical Center of Louisiana Foundation and the Tulane and Louisiana State University Schools of Medicine. I was the eighth recipient of the award, which recognizes contributions to the former Charity Hospital and its teaching, research, and patient care missions in support of the two medical schools."

1963

Norman Wilson, Jr.

"I'll continue to practice psychiatry until September 2011, and then I'll spend more time volunteering and visiting my son and two

PHOTOS: JAN REISS

grandchildren. I went backpacking in Banff and Jasper parks in Canada this past summer."

Robert Rawitscher
has been named to the medical advisory board of Organ Transport Systems in Frisco, Texas

1968

Sarah Donaldson
"While I continue to work full-time as professor of radiation oncology at Stanford, I also have a leadership position at the Radiologic Society of North America, currently serving as chairman of the board—and having a great time! Outside of Stanford and RSNA I've discovered biking as a relaxing way to exercise."

1971

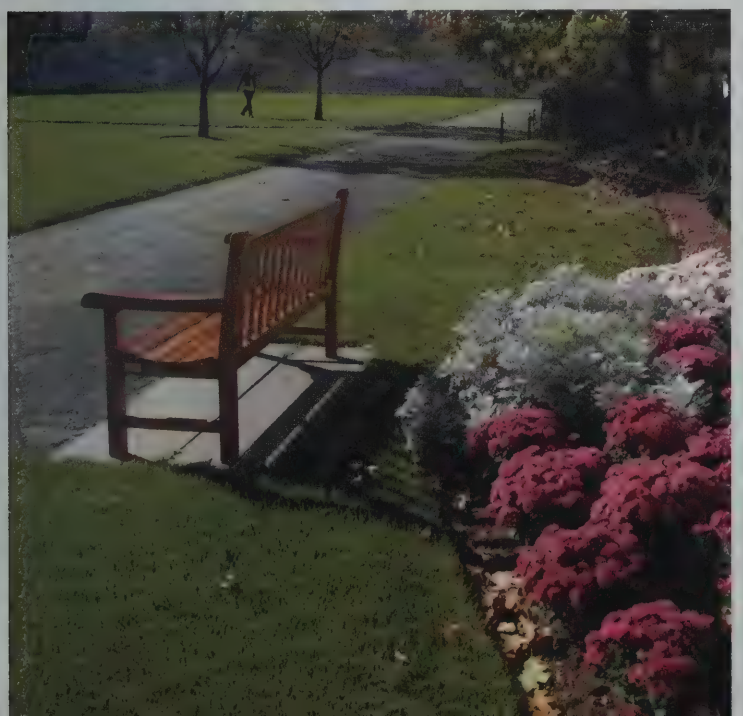
Harvey V. Fineberg
has been named to receive the 2011 Frank A. Calderone Prize from Columbia University's Mailman School of Public Health.

Joel Greenberger
"My son Ben has been accepted to HMS, Class of 2015, and will enter this fall. My daughter Emily, a member of Dartmouth Medical School's Class of 2013, is in Botswana as a Doris Duke Fellow in global health. Josh continues in Pitt Pharmacy School, and Rachel received her MBA in May 2011. My wife, Cathy, retired from internal medicine. I continue to serve as chair of radiology oncology at Pitt Med School and to develop radiation countermeasures for the National Institutes of Health."

1972

Edward J. Benz, Jr.
is the 2011 recipient of the Margaret L. Kripke Legend Award for Promotion of Women in Cancer Medicine and Cancer Science, from the University of Texas MD Anderson Cancer Center.

Peter Weller
received an NIH MERIT (Method to Extend Research in Time) award from the National Institute of Allergy and Infectious Diseases.



1973

Stephen Bergman
"The play my wife, Janet Surrey, and I (under my pen name, Samuel Shem) wrote about Alcoholics Anonymous, *Bill W. and Dr. Bob*, is returning to Broadway. Last year I was astonished and gratified to be the HMS commencement speaker. Live long enough, you see everything!"

Donald Weaver
"After 35 and a half years as a commissioned officer in the U.S. Public Health Service, I retired on January 1, 2011. I'm exploring ways to expand access to primary care for underserved communities and vulnerable populations and to eliminate health disparities. Jane and I continue to enjoy time with our daughters, their husbands, and our grandchildren, William and Elle."

1974

David Blumenthal
has been named chairman of the Commonwealth Fund Commission on a High Performance Health System.

James Maguire
returned to his high school in Easton Pennsylvania to receive an alumni honor on May 6, 2011.

1975

José Rigau
"With Don Peterson and Rosemary Case in Philadelphia this past May, we shared a great meal and an even better time, with many thoughts of our HMS classmates."

1976

Deborah Frank
has been named as the first incumbent to the Professorship in Child Health and Well-Being at the Boston University School of Medicine.

1977

Juan Albino
"My oldest son, Juan, practices law in Puerto Rico; my oldest daughter, Isabel, practices law in New York; and my second son is an internal medicine intern with the VA in San Juan, Puerto Rico. So far I have been fortunate with my children. I still have a teenager in high school."

Nancy Turner Banks
has won a gold medal for outstanding book of the year, from the Independent Publisher Association for *AIDS, Opium, Diamonds and Empire: The Deadly Virus of International Greed.*

Mark Klausner
has been named chief medical officer for CorMedix Inc. in Bridgewater, New Jersey.

1978

Marshall Ruffin, Jr.
has been named chief technology officer for Inova Health System in Falls Church, Virginia.

Earl Steinberg
was named executive vice president for innovation and dissemination, and chief of Geisinger Healthcare Solutions Enterprise

CLASS NOTES

NEWS FROM ALUMNI

at Geisinger Health System in Danville, Pennsylvania.

David Stern
has accepted the position of executive dean and vice chancellor for health affairs of the College of Medicine at the University of Tennessee Health Science Center.

1979

Kenneth Robinson
was recently appointed public health policy adviser to Shelby County, Tennessee.

1982

Steven Goldstein
has been appointed provost of Brandeis University.

Sundeep Khosla
was elected president of the American Society for Bone and Mineral Research.

1987

Louis Aviles
"We have two kids in college and our youngest is a high-school junior. My wife, Abby, and I have begun to do medical mission trips. In the course of one year we were blessed to work in Nicaragua, Haiti, and now to Israel next month. These have been amazing experiences and we highly recommend them. Use your talents; use your gifts!"

Valerie Montgomery Rice
has been named Dean and Executive Vice President of Morehouse School of Medicine.

1989

Pablo Lapuerta
has been appointed chief medical officer at Lexicon Pharmaceuticals in The Woodlands, Texas.

A. Gregory Sorensen
has been appointed chief executive officer of Siemens Healthcare USA.

1990

Eric Pierce
joined the Massachusetts Eye and Ear Infirmary's Department of Ophthalmology in September as associate director of the Berman-Gund Laboratory for the Study of Retinal Degenerations.

1992

Vivian Lee
has been appointed senior vice president for health sciences at the University of Utah, where she will also will serve as dean of the University's School of Medicine and as chief executive officer of University of Utah Health Care.

Samir Shah
was named as one of "Rhode Island's Top Docs" in a poll of physicians taken by *Rhode Island Monthly* magazine.

1993

Joan Lo
"I am in my eighth year at Kaiser Permanente Northern California Division of Research, where I hold the position of assistant program director for the Kaiser Permanente Oakland Internal Medicine Residency Program."

1994

Atul Gawande
recently received the inaugural athenahealth Vision Award. Gawande has also been named among the *Boston Globe*'s 100 most innovative people in Massachusetts.

Seth Karp
has been named head of Vanderbilt University Medical Center's Transplant Center.

1997

Randall King
has been named scientific cofounder of Proteostasis Therapeutics in Cambridge.

1999

Paveljit Bindra
has been named chief medical officer/chief medical information officer at Citrus Valley Health Partners in West Covina, California.

2000

Siddhartha Mukherjee
won a 2011 Pulitzer Prize for his recent book, *The Emperor of All Maladies: A Biography of Cancer.*

2003

L. Thomas Richards
has been appointed president of TessArae, LLC, in Potomac Falls, Virginia.

2006

William Polkinghorn
received a creativity award for advanced prostate cancer research from the Prostate Cancer Foundation.

PHOTO: JAN REISS

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1941

William Daniel

Died on April 6, 2011, at the age of 94, in Charlottesville, Virginia, from complications of pneumonia. Daniel served as a U.S. Army medical officer in the Aleutian Islands during World War II. He practiced gynecological surgery at Memorial Sloan-Kettering Hospital in New York. Daniel was predeceased by his first wife, Susan, and his daughter, Alice. He is survived by his wife of 48 years, Stella; children Bill, Katie, and Tom; six grandchildren; and four great-grandchildren.

Stanford Shea Kroopf

Died on April 18, 2011, at the age of 93. Kroopf served in the Tropical Medicine Division of the U.S. Army Air Force during World War II. He was professor emeritus of internal medicine and cardiology at the Stanford University School of Medicine. He maintained a private practice in internal medicine, with a specialty in cardiology, and founded and chaired a coronary care unit at Stanford Hospital. Kroopf was predeceased by his wife, Barbara (Bobbie). He is survived by his daughter, Connie; his sons, Scott and Sandy; five grandchildren; and two great-grandsons.

John G. Sholl, III

Died on March 21, 2011, at the age of 96, in Peoria, Illinois. Sholl was a captain and medic in the U.S. Army during World War II. He maintained a private practice in internal medicine in Cleveland, Ohio, for 35 years. He served as an associate professor of medicine at Case Western Reserve University School of Medicine, and later was professor of medicine at the University of California San Diego School of Medicine. Sholl was predeceased by his wife, Marjorie. He is survived by his children, John, Debora Humphreys, Robert, David, and Rebecca Baer; 11 grandchildren; and 9 great-grandchildren.

1942

William K. Hall

Died on March 2, 2011, at the age of 92, in St. Louis, Missouri. Hall served in the U.S. Navy Medical Corps for 20 years, retiring as a captain. He maintained a private practice in dermatology in St. Charles, Missouri, and was assistant professor of medicine emeritus in dermatology at Washington University School of Medicine in St. Louis. Hall is survived by two nephews and five nieces.

1943

Chester A. Wiese, Jr.

Died on May 31, 2011, at the age of 94, in Fort Myers, Florida. Weise served in World War II in the U.S. Navy Medical Corps at Normandy and in Okinawa. He was assistant chief of surgery at Hartford Hospital before retiring in 1988, and was an associate professor of surgery at the University of Connecticut School of Medicine. He was predeceased by his partner of 43 years, Charles Hamblen, and is survived by his stepbrother, Robert Witbeck; his nieces, Anne Hemmingway, Claire Porter, Jane Berry, Amey Witherbee, Parsons Clark, Martha Chamberlain, Pamela Brasset, and Susan Patterson; and his nephews, Robert Pease, Hunter Brown, and Clifford Brown.

1945

L. Eric Liberman

Died on May 1, 2011, at the age of 89. Liberman served as a U.S. Army medical officer in post–World War II Japan, and in the U.S. Air Force Medical Corps during the Korean conflict. He maintained a private practice in internal medicine in Torrington, Connecticut, until 1959, when he moved to Portland, Oregon, to work with Kaiser Permanente. Specializing in endocrinology and metabolism, Liberman was an affiliate associate professor in the endocrinology division of the Oregon Health and Science University's Department of Medicine. He is survived by his wife of 62 years, Suzanne; his sons, Adam and Lev; and two grandchildren.

Robert A. McNaughton

Died on April 13, 2011, at the age of 90, in Coconut Grove, Florida. McNaughton maintained a private gastroenterology practice in Miami for 40 years, and was a founder of the Doctors Hospital in Coral Gables, Florida. He taught gastroenterology on a voluntary basis at the University of Miami Medical School. McNaughton is survived by his wife, Patricia; his son, Robert Jr. (Sandy); his daughter, Marlee Matheson; and four grandchildren.

1946

Thomas Joseph Donovan

Died on April 6, 2011, at the age of 88, in Bloomfield, Connecticut. Donovan was a pioneer in cardiac surgery research and practice, performing the first open-heart surgery at Hartford Hospital in 1959 and the first mitral-valve replacement surgery there in 1962. In retirement, he taught at the surgery clinic at the West Haven VA Hospital, taught anatomy at the University of Connecticut Medical School, and continued basic research in vascular surgery. Over his long career he collected historical surgical instruments, devices, and prototypes; the collection is permanently housed in the Cardiovascular Surgery Department at Brigham and Women's Hospital. He is survived by his wife of 57 years, Harriet; his daughters, Susan, Kathryn Wiegand, Nancy, and Jane Peacock; his sons, Thomas, Paul, and Joseph; his brother, James '52; and 14 grandchildren.

Noble S. Maluf

Died on March 11, 2011. Maluf was chief of urology at the VA Hospital and assistant professor at Baylor University College of Medicine, in Houston, Texas. He later served as a surgeon at Hollywood-Presbyterian Hospital in Los Angeles, and was professor of nephrology at Case Western Reserve University. Maluf is survived by his daughter, Anouchka (Annie), and two grandchildren.

1947

Fred Starr Endsley, Jr.

Died on April 9, 2011, at the age of 87. Endsley served in the Korean War as a surgeon in the U.S. Navy. He practiced surgery in Provo, Utah; Santa Barbara, California; and Chicago, and he served on the medical school faculty of Northwestern University. He was predeceased by his wife, Patricia, and his son Fred. He is survived by his son Scott; his daughter, Ellen Garland; seven grandchildren; and two great-grandchildren.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

W. Jape Taylor

Died on March 22, 2011, at the age of 86, at his home in The Village in Gainesville, Florida. Taylor was the first chief of cardiology at the University of Florida Medical School. He was predeceased by his wife of 60 years, Audrey. He is survived by his sons, J. Holley, Andrew, Richard, and D. Lee; and three grandchildren.

1948

Frank D. Bates

Died on May 23, 2011, at the age of 85, at his home in Center Sandwich, New Hampshire, of chronic lung disease. Bates earned a Bronze Star while a captain in the U.S. Army Medical Corps during the Korean War. He maintained an orthopedics practice at several Boston-area hospitals, including Winchester Hospital, where he was chief of orthopedics. Bates was predeceased by his first wife, Helen. He is survived by his second wife, Elizabeth (Lib); his children, Sarah, Gretchen, and Chris; and four grandchildren.

Lyman Avard Fulton

Died on May 2, 2011, at the age of 85, in Johnson City, Tennessee. Fulton served in the U.S. Navy during World War II and was a member of the U.S. Navy Reserve during the Korean War. He also served in the U.S. Army Medical Corps on active duty in Japan. He was an assistant professor of medicine at the University of Utah Medical School before returning to Tennessee, where he maintained a private practice in internal medicine in Johnson City for 10 years. He was director of the medical education and internal medicine residency program at Louise Obici Memorial Hospital in Suffolk, Virginia, and then returned to Johnson City, where he was on staff at the Mountain Home VA Center until retiring as chief in 1991. He is survived by his wife, Patty; his sons, Lyman III and Kerwin; his daughter, Hazel Robinson; and two grandchildren.

Walter C. Rattan

Died on March 8, 2011, at the age of 84, at his home in Kenosha, Wisconsin. Rattan served as a captain in the U.S. Air Force. As an obstetrician and gynecologist, Rattan was an advocate for women's reproductive rights, and co-founded the Planned Parenthood Clinic of Kenosha. He practiced medicine for 32 years until his retirement in 1986. In 1998, the State Medical Society of Wisconsin Fifty Year Club recognized his service to the profession. He was also awarded recognition for his outstanding service to St. Catherine's Hospital from 1954 to 1986. He is survived by his wife of 62 years, Joanne; his sons, Neil, Eric, and Mark; his daughter, Martha Tubinis; and nine grandchildren.

Joseph Claude Finney

Died on March 3, 2011, at the age of 83, after a long illness. Finney served in the U.S. Coast Guard during the Korean War and retired from the U.S. Army as a colonel in 1987. His medical specialty was psychiatry, but he was also licensed to practice clinical psychology, law, family counseling, and investment advising. He established and directed the first mental health clinic in Urbana, Illinois; taught psychology at the University of Illinois; was the first director of mental health research for the new state of Hawaii in 1960; and taught at the University of Hawaii. In 1963 he moved to Lexington, Kentucky, where he taught at the University of Kentucky for 18 years. Finney was predeceased by his wife of 51 years, Mary Elizabeth. He is survived by his children, Michael, John, Carol, and Ellen; and four grandchildren.

James Basil Gabriel

Died on March 9, 2011. Gabriel served as an attending physician at Roosevelt Hospital in New York City beginning in 1962. He is survived by his wife, Nancy; his daughter, Lynn Angelus; his son, Jim; and three grandchildren.

John "Jack" Reardan

Died on May 10, 2011, at the age of 85, at his home in Elk Grove, California, of multiple myeloma. Reardan served as a troopship physician in the U.S. Navy during the Korean War. He practiced internal medicine, cardiology, and nephrology at Mercy General and Sutter Community Hospitals in California for more than 40 years, and at the University of California, Davis, Medical School since its inception in 1968. He was a recipient of the Golden Stethoscope Award from the Sacramento–El Dorado County Medical Society. Reardan is survived by his wife, Nancy; his children, Susan O'Neill, Dayton, Linda Kirkpatrick, John, and Frank; and nine grandchildren.

Peter G. Robbins

Died on May 9, 2011, at the age of 86, in Portland, Maine. Robbins was in the U.S. Navy Reserves when the Korean War began in 1950, and he volunteered for duty as a battalion surgeon with the U.S. Marine Corps. He was awarded the Bronze Star for his service. He established an obstetrics and gynecology practice in Boston, and served on the faculty of Harvard Medical School. After many years in private practice, he was recruited to the original panel of physicians for Harvard Community Health Plan, where he worked until his retirement in 1990. Robbins is survived by his wife, Merrill; his sons, Peter and William; his daughters, Merrill Woodworth and Jennifer Robbins; and five grandchildren.

Charles Howard Wells

Died on April 27, 2011, at the age of 87, in Rockport, Massachusetts. Wells was commander of the Cutler Army Hospital at Fort Devens, Massachusetts, until his retirement. Previously, he served as a medical officer in the U.S. Army for 30 years, starting with the Army's wartime medical program during World War II and later serving as a medical officer in Korea and Vietnam. Wells was predeceased by his first wife, Marie. He is survived by his second wife, Marie; his children, Charles, Jr., Craig, and Christine; his stepchildren, Drew Williams and Ingrid Viventi; many grandchildren; and several great-grandchildren.

1950

Robert Ray Aycock

Died on April 28, 2011. In 1955, Aycock moved to San Francisco, where he maintained a practice in internal medicine for many years. Early in his practice he affiliated with the medical department of the Del Monte Corporation and ultimately became medical director for the food company's worldwide medical facilities. Aycock was predeceased

by his parents and two sisters. He is survived by his partner of 58 years, Donald James Clark.

1951

Lawrence Martin Baker III

Died on May 25, 2011, at the age of 85, in Chestertown, Maryland. Baker served in the Pacific theater in the U.S. Army during World War II. He practiced general and thoracic surgery at the former Kent General Hospital in Dover, Delaware. Baker is survived by his wife of 62 years, Margaret (Margot); four daughters, Christine Brockmeyer, Nancy Coffin, Marianne Kitchell, and Barbara; nine grandchildren; and two great-grandchildren.

1952

Maurice "Josh" Jurkiewicz

Died on May 29, 2011, at the age of 87, at Emory Midtown Hospital in Atlanta. Jurkiewicz served with the U.S. Navy Reserves in Normandy post–World War II. He was chief of plastic surgery at the University of Florida from 1959 to 1971 and chief of surgery at the VA Medical Center in Gainesville from 1968 to 1971. He then became chief of reconstructive/plastic surgery at the Emory University School of Medicine, a post he held until 1993. He was a consulting plastic surgeon to Walter Reed Army Hospital in Washington, DC. Jurkiewicz was predeceased by his wife of 57 years, Mary. He is survived by his daughter, Beth Wilson; his son, Chris; and two grandchildren.

Joe Wilber

Died on April 3, 2011, at the age of 86, in Atlanta, from complications of amyotrophic lateral sclerosis. Wilber served in the U.S. Army during World War II. He maintained a private practice in internal medicine prior to beginning his public health career as head of Georgia's infectious disease program. He started the nation's first public hypertension program and a statewide diabetes program in Georgia. In retirement, Wilber helped found the Good Samaritan Health and Wellness Center in Jasper, Georgia. He is survived by his wife of 58 years, Patricia; his sons, Joe, John, and Bryan; his daughter, Martha; and seven grandchildren.

1953

Richard E. Hughes

Died on March 1, 2011, at the age of 87, at his home in Oxford, Maryland. Hughes served in the U.S. Army in Burma during World War II. He was an instructor in surgery at the George Washington University Hospital in Washington, DC, and served as assistant chief of surgery at the DC Chest Hospital in Glendale, Maryland. In 1962, he began his practice as a cardiothoracic surgeon at the former Peninsula General Hospital in Salisbury, Maryland. In 1964, Hughes helped establish the intensive care unit at Peninsula General, where he also served as chairman of the Department of Surgery and created the Division of Thoracic and Cardiovascular Surgery. He is survived by his wife of 49 years, Doris; his four daughters, Amy Hirsch, Susan Mertes, Sarah, and Abigail Marsh; five grandchildren; and two step-grandchildren.

1959

Frederick Sherman Baker

Died on March 28, 2011, at the age of 77. Baker served as a surgeon at the U.S. Army hospital in Yokohama, Japan, during the Vietnam War. He practiced colon and rectal surgery in Sacramento, California, for more than 40 years. Baker is survived by his wife, Gaye; his sons, Eric, Henry, and Fred; and six grandchildren.

Ira Marks

Died March 8, 2011, at his home in Old Chatham, New York. Marks served as president of his Harvard Medical School class. From 1962 to 1964, he practiced pediatrics as a captain in the U.S. Air Force at Andrews Air Force Base in Washington, DC, earning the Air Force Commendation Medal for meritorious service. A pediatrician in Chatham, New York, for more than 40 years, Marks began working at Columbia Memorial Hospital in Hudson, New York, in 1964, and served as chief of pediatrics from 1978 to 1989. Marks is survived by his wife of 49 years, Susannah; three children, Sarah, Ilana, and Jared; and seven grandchildren.

1960

Robert Frank Biehl

Died on March 22, 2011, at the age of 76, at his home in Springfield, Illinois. Biehl served in the U.S. Navy Medical Corps for 33 years, retiring as a captain in 1987. He was also pediatric advisor to the Surgeon General of the Navy and chief of pediatrics at the National Naval Medical Center in San Diego. He is survived by his wife of 52 years, Wini; four children, Thomas, Gretchen Edison, Andrew, and Ellen Fung; and seven grandchildren.

1964

David Ward Havens

Died on February 28, 2011, at the age of 72. Havens served as a captain in the U.S. Air Force from 1968 to 1970. He maintained a private psychiatric practice in Boston for 22 years, and in Hendersonville and Springfield, Tennessee, for 15 years. He is survived by his wife of 48 years, Sarah (Sally); his sons, Andrew and John; and three grandchildren.

1971

John Gary Curd

Died on April 20, 2011, at the age of 65, at his home in Hillsborough, California. Curd served as president of Scripps Green Hospital in La Jolla, California, where he spent 16 years in clinical practice and research in rheumatology. In 1991, he transitioned into the biotechnology industry, and most recently was president and chief medical officer of Threshold Pharmaceuticals. He is survived by his wife of 40 years, Karen; his four children, Alison Lowery, Jonathan, Edward, and Bethany; and three grandchildren.

1976

James Lyons III

Died on May 12, 2011, at the age of 60, at his home in Carlsbad, California. A psychiatrist, Lyons was on staff at Napa State Hospital in Napa, California, for 25 years. After retirement, he worked for Kaiser Permanente in Carlsbad. He is survived by his children, Stacy and Kevin.

PHOTO: COURTESY OF THE HOUGHTON LIBRARY, HARVARD UNIVERSITY

TAKING A HISTORY

PROFILE OF SUZIE BROWN

HEART AND SOUL: Suzie Brown rocks a music career and a cardiology practice in parallel worlds.

CLAIMS TO FAME: Attending physician in the Division of Cardiology at Albert Einstein Medical Center in Philadelphia, singer–songwriter, and recording artist

EARLY ROOTS: The next time you visit a Starbucks, listen closely and you just might hear Suzie Brown's *Heartstrings*, a recent album of original music. Although her day job finds her attending to the demands of a clinical position in cardiology, Brown '02 pours equal effort into her blossoming musical career, a passion that began early, when, as a child, she sang Top 40 songs in the family basement. Yet Brown was timid about going public with music until long after her basement days, traveling a traditional hyperachiever route, excelling in math and softball.

A LITTLE BIT COUNTRY...: Brown's musical sensibility veers toward the twangy bluesy sounds of two of her muses, Bonnie Raitt and Gillian Welch. She started writing her own songs just a few years ago, after she sang John Prine's *Angel from Montgomery* at a friend's wedding and was inspired by the response to her performance. Brown has since opened for Lyle Lovett, been named "Best of Philly" in the music category by *Philadelphia* magazine, and released two albums of original music. Brown enjoys the science she finds in music, and she even uses spreadsheets to track her songwriting and performing schedule. With little formal training in music, she prefers to write what she hears and compose the music as she goes, intuitively finding rhythms and harmonies that work, a process unlike the 15 years of medical training that led to her clinical appointment.

...A LITTLE BIT CARDIO: Cardiology was Brown's first love in medical school. "I couldn't wait to go to school to learn more," she says. "I loved cardiology. The mechanical physiology just felt intuitive." Brown is passionate about medical care and believes her patients appreciate her manner and skill in treating them. "I'm proud that in some ways I'm tough and rigorous. And when I'm with a patient, I can put aside everything else that's going on."

HAPPY TOGETHER: So how does Brown meld two careers together so well? For one thing, she is able to support her music career by working part-time as a cardiologist. This arrangement has freed her as a musician and allowed her to write for herself rather than for a record label's marketing department. Brown says that her medical training taught her to have a sense of fearlessness about trying new things, such as beginning a musical career. Years of rotating through different specialties, repeatedly progressing from ignorance to competence, helped her feel comfortable with learning how to tackle the seemingly impossible. Brown is grateful for how both careers have been unfolding. "I wake up most days," she says, "and wonder if this is really my life."

—*Susan Karcz*

PHOTO: ZOEY SLESS-KITAIN

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